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The Honorable Sherry R. Fallon
United States District Court for the District of Delaware
844 N. King Street
Wilmington, DE 19801-3555

VIA ELECTRONIC FILING
REDACTED -
PUBLIC VERSION

Re: *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 23-975-RGA-SRF

Dear Judge Fallon:

United Therapeutics Corporation ("UTC") regrets that the parties are before this Court with motions to strike reply expert reports—UTC believed that the issues were more properly addressed in pretrial *Daubert* and motion *in limine* practice before Judge Andrews. Nevertheless, because Liquidia insisted upon asking the Court to strike at least two UTC expert reports, UTC respectfully moves to strike portions of Dr. Nicholas Hill's reply report (in particular, ¶¶ 16-17, 77-81, 94-96, 106, 110-112, and 148-79) as untimely and beyond the scope of a proper reply. UTC also conditionally moves to strike ¶¶ 47-54 and 95-289 of Dr. Stephan Ogenstad's reply report.[1]

Dr. Hill is one of Liquidia's two clinical experts in this matter. His reply report improperly introduced new opinions on inequitable conduct, prior sale, and public use that were not disclosed in his opening report, even though Liquidia bears the burden of proof on those issues. These opinions are improper and prejudice UTC by purporting to shift the burden of proof on invalidity to UTC and depriving UTC's experts of the opportunity to fully rebut Dr. Hill's opinions.

Dr. Ogenstad is Liquidia's biostatistics expert. In a parallel motion also due to be filed this morning, Liquidia promised to move to strike reply opinions offered by UTC's biostatistician, Dr. Thisted, as untimely and duplicative. These attacks lack merit and UTC will address them in its rebuttal letter. But based on Liquidia's alleged rationale, all its criticisms apply with equal force to Dr. Ogenstad. UTC does not believe it is appropriate to strike ***either*** Dr. Thisted's or Dr. Ogenstad's reply opinions. However, should the Court decide to strike Dr. Thisted's opinions, UTC submits that the same standard would justify striking Dr. Ogenstad's opinions.

I. Dr. Hill's Reply Opinions on Validity and Inequitable Conduct are Untimely

Dr. Hill's reply report improperly offers new opinions concerning invalidity and inequitable conduct—issues on which Liquidia bears the burden of proof. These opinions are untimely under Fed. R. Civ. P. 26(a)(2), beyond the proper scope of a reply, and should be excluded. Rule 26(a)(2)(B)(i) requires an expert witness to disclose a report that contains a "complete statement of all opinions the witness will express and the basis and reasons for them." Rule 26(a)(2)(D) similarly requires that parties disclose expert testimony "at the times and in the

[1] These paragraphs are subject to parallel *Daubert* motions pending before Judge Andrews.

sequence that the court orders." When expert testimony is not timely disclosed, the court has the authority to exclude it from evidence under Fed. R. Civ. P. 37(c)(1). *TQ Delta, LLC v. Adtran, Inc.*, C.A. No. 14-954-RGA, 2021 WL 1200594 (D. Del. Mar. 30, 2021) (citing Fed. R. Civ. P. 37(c)(1)).

Rule 26(a)(2) precludes an expert from introducing new arguments in a rebuttal or reply report on issues on which the offering party bears the burden of proof. "'[R]ebuttal evidence is limited to that which is precisely directed to rebutting new matter or new theories presented by the [opposing party's] case-in-chief' and 'is not an opportunity for the correction of any oversights in the [offering party's] case-in-chief.'" *Wang v. Injective Labs Inc*., C.A. No. 22-943-WCB, 2025 WL 775530, at *2 (D. Del. Mar. 11, 2025). Courts routinely exclude expert testimony that runs afoul of this principle. *See, e.g., id.* at *2 (excluding new theory in rebuttal report that "would need to be presented in [the offering party's] case-in-chief, given that [the offering party] has the burden of proof"); *In re Asbestos Prods. Liab. Litig. (No. VI)*, C.A. No. 09-74351X, 2012 WL 661673, at *3-4 (E.D. Pa. Feb. 8, 2012), *report and recommendation adopted sub nom. In re Asbestos Prods. Liab. Litig. (No. IV),* No. 09-74410, 2012 WL 661660 (E.D. Pa. Feb. 29, 2012); *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, C.A. No. 03 -7713, 2005 WL 1300763, at *2-3 (N.D. Ill. Feb. 22, 2005); *Wisconsin Alumni Rsch. Found. v. Apple, Inc*., 261 F. Supp. 3d 900, 918 (W.D. Wis. 2017), *rev'd as to other grounds*, 905 F.3d 1341 (Fed. Cir. 2018). Dr. Hill's reply report improperly seeks to do exactly what these authorities prohibit: correct oversights and fill gaps in his opening opinions on inequitable conduct and invalidity.

For inequitable conduct, Liquidia must prove that the allegedly withheld references are not cumulative over information the patent examiner already possessed. *Intermec Techs. Corp. v. Palm Inc*., 738 F. Supp. 2d 522, 561 (D. Del. 2010), *aff'd*, 466 F. App'x 881 (Fed. Cir. 2012). Dr. Hill, however, failed to address cumulativeness in his opening report and raised the issue for the first time in reply. *See* Ex. 1 (Hill Op. Rpt.) at ¶¶ 213-68; Ex. 2 (Hill Reply Rpt.) at ¶¶ 149-70; Ex. 3 (Hill Dep. Tr.) at 40:17-41:24. Because he failed to address the matter in his opening report, the new opinions regarding cumulativeness in his reply report are untimely and should be struck.

Regarding invalidity under the public use and/or the on-sale bars, Liquidia must prove that the claimed invention was ready for patenting because it was either reduced to practice or disclosed in enabling documents or drawings. *Creo Prods., Inc. v. Presstek, Inc*., 166 F. Supp. 2d 944, 967 (D. Del. 2001), *aff'd*, 305 F.3d 1337 (Fed. Cir. 2002). If relying on reduction to practice, Liquidia bears the burden to show that the invention worked for its intended purpose. *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1332 (Fed. Cir. 2019). Dr. Hill's opening report alleged invalidity under the prior sale and prior public use bars and relied ***only*** on reduction to practice to establish the ready for patenting element. *See* Ex. 1 at ¶ 172. However, Dr. Hill did not analyze whether the invention worked for its intended purpose. *Id.*; Ex. 3 at 28:21-32:22. Further, Dr. Hill's analysis of prior public use failed to address the required element of whether the claimed invention was put in the possession of the public. *See, e.g.*, Ex. 1 at ¶ 132; *Dey, L.P. v. Sunovion Pharms., Inc.*, 715 F.3d 1351, 1359 (Fed. Cir. 2013). Liquidia used Dr. Hill's reply report as an opportunity to correct these foundational oversights, which is improper and prejudices UTC. *Wang*, 2025 WL 775530, at *2; Ex. 2 at ¶¶ 77-81 (public possession), ¶¶ 110-111 (enabling documents and drawings), ¶¶ 94-96, 106, 112 (invention was demonstrated to work for its intended purpose), ¶¶ 17, 148-79 (cumulativeness). Because Dr. Hill said nothing in his opening report about enabling documents and drawings, the public's possession of the invention, and the invention working for its intended purpose, he should not be able to correct these oversights through his reply report.

Under Rule 37(c)(1), "[i]f a party fails to provide information … as required by Rule 26(a) or (e), the party is not allowed to use that information … to supply evidence on a motion, at a hearing, or at a trial, unless the failure was substantially justified or is harmless." "Rule 37 is written in mandatory terms, and is designed to provide a strong inducement for disclosure of Rule 26(a) material." *Wang*, 2025 WL 775530, at *3 n.1 (quoting *Newman v. GHS Osteopathic, Inc.*, 60 F.3d 153, 156 (3d Cir. 1995)). Third Circuit courts apply the *Pennypack* factors to resolve disputes under Rule 37: (1) the prejudice or surprise to the party against which the evidence would be admitted; (2) the ability of that party to cure the prejudice; (3) the extent to which waiver of the rule in question would disrupt the orderly and efficient trial of the case; (4) bad faith or willfulness on the part of the party offering the evidence in failing to comply with the court order, and (5) the importance of the excluded evidence.[2] *Id.* at *2 (citing *Meyers v. Pennypack Woods Home Ownership Assn.*, 559 F.2d 894, 904 (3d Cir. 1977) and *Quinn v. Consolidated Freightways Corp. of Del.*, 283 F.3d 572, 577 (3d Cir. 2002)). In the case of "sophisticated, complex litigation involving parties represented by competent counsel," the court should be "less indulgent in [applying *Pennypack*] and more willing to exclude evidence without a strict showing that each of the … factors has been satisfied." *Id.* at *3; *see also TQ Delta, LLC*, 2020 WL 4529865, at *2.

The *Pennypack* factors justify exclusion here. The late disclosure of Dr. Hill's opinions is *per se* surprising because "it would be surprising to receive an affirmative … theory served under the guise of a rebuttal report after the [party] had failed to provide [the] affirmative theory in an initial report." *Wang*, 2025 WL 775530, at *4. Dr. Hill's failure to address all of the required elements of inequitable conduct, public use, and prior sale in an opening report is also prejudicial because Liquidia and Dr. Hill were already privy to the responsive opinions of UTC's experts and thus had an advantage when developing Dr. Hill's complete invalidity and inequitable conduct positions. *Id.* By contrast, UTC's experts drafted their rebuttal opinions without the benefit of Dr. Hill's complete analysis and were not able to respond to Dr. Hill's reply report. *In re Asbestos Prods. Liab. Litig. (No. VI),* 2012 WL 661673, at *3-4. Even so, allowing UTC's experts a supplemental response ***now*** would not cure the prejudice to UTC, as it would not reverse Dr. Hill's advantage in drafting his report, and UTC would be required to spend time drafting supplemental reports that it could otherwise spend on other pre-trial matters. *Wang*, 2025 WL 775530, at *4.

Moreover, Liquidia's late disclosure of opinions on issues for which it has the burden of proof is "part of a developing pattern of untimeliness," which raises an inference of bad faith and weighs in favor of excluding the late opinions. *Id.* For example, [redacted] Ex. 4. [redacted] Ex. 5. This conduct evinces a general disregard for the timely and orderly disclosure of information.

For these reasons, the improper opinions set forth in ¶¶ 16-17, 77-81, 94-96, 106, 110-112, and 148-79 of Dr. Hill's reply report should be excluded.

[2] Sitting by designation in *Wang*, Judge Bryson noted that *Pennypack* is "in tension with the plain language of Rule 37(c)," which "is written in mandatory terms, and is designed to provide a strong inducement for disclosure." 2025 WL 775530, at *3 n.1.

II. If the Court Grants Liquidia's Motion to Strike as to Dr. Thisted, Sections of Dr. Ogenstad's Reply Report Should Also be Stricken

Liquidia has informed UTC that it seeks to strike opinions in Dr. Thisted's Reply Report that are (i) allegedly untimely opinions on infringement issues where UTC bears the burden of proof, or (ii) allegedly duplicative of opinions offered in the opening and/or reply reports of UTC's clinical expert, Dr. Nathan. Liquidia's position is both meritless and hypocritical. As UTC will explain in its forthcoming rebuttal letter, Liquidia's motion to strike should be denied because Dr. Thisted's reply opinions are neither untimely nor duplicative. Further, to the degree the Court credits those assertions, both also apply to the reply invalidity report of Liquidia's own biostatistics expert, Dr. Ogenstad. Liquidia cannot seek to exclude Dr. Thisted's reply opinions without also implicating Dr. Ogenstad's reply opinions. To be clear, UTC maintains that neither Dr. Ogenstad's nor Dr. Thisted's reply opinions should be stricken. UTC sought to avoid burdening the Court with this unnecessary dispute by proposing to Liquidia that the parties either (i) forgo this motion to strike; or (ii) incorporate any arguments the parties would make here into their parallel *Daubert* motions before Judge Andrews. Liquidia rejected both proposals. This left UTC no choice but to submit a reciprocal motion regarding Dr. Ogenstad.

First, Liquidia asserts that Dr. Thisted's reply opinions regarding infringement are untimely because he did not submit an opening report and UTC bears the burden on infringement. The same, however, is true of Dr. Ogenstad's reply opinions, which relate to invalidity. *See, e.g.*, Ex. 6 at ¶¶ 47-54, 95-289. While Liquidia submitted opening reports on invalidity from other experts, Dr. Ogenstad submitted only a reply report. This prejudiced UTC by ensuring that UTC's own biostatistics expert, Dr. Thisted, had no opportunity to address Dr. Ogenstad's opinions in a subsequent report. Thus, if the Court strikes Dr. Thisted's infringement opinions as untimely, it should similarly strike the invalidity opinions in ¶¶ 47-54, 95-289 of Dr. Ogenstad's reply report.

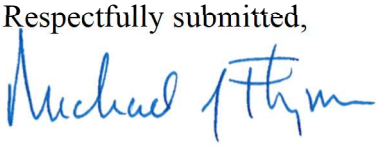
Second, Liquidia argues that Dr. Thisted's infringement opinions are duplicative of those offered by UTC's clinical expert, Dr. Nathan. This alleged defect is, again, present in Dr. Ogenstad's reply opinions on validity. For example, Dr. Ogenstad's validity opinions merely repeat and agree with Liquidia's clinical expert, Dr. Channick, regarding the same exact references and evidence. Ex. 6 at ¶¶ 47-54, 95-289. Similarly, Drs. Channick and Ogenstad offer overlapping opinions on priority in response to UTC's other clinical expert, Dr. Wertheim. *Compare* Ex. 6 at ¶¶ 258-89 *with* Ex. 8 (Channick Rep. Rpt.) at ¶¶ 86-112, 123-24, 134-37. Dr. Ogenstad even admitted at his deposition that he has no medical training or experience treating PH-ILD patients and relied on Dr. Channick's clinical opinions when drafting his reply report. Ex. 7 (Ogenstad Dep. Tr.) at 47:9-24, 75:7-78:20. Accordingly, should the Court decide to exclude Dr. Thisted's infringement opinions as duplicative, it should exclude the validity and priority date opinions in ¶¶ 47-54, 95-289 of Dr. Ogenstad's reply report for the same reason. Ex. 6.[3]

III. Conclusion

For the reasons set forth above, UTC respectfully requests that this Court strike ¶¶ 16-17, 77-81, 94-96, 106, 110-112, and 148-79 of Dr. Hill's reply report. Additionally, UTC respectfully requests that this Court apply the same standard of review to the reply opinions offered by both parties' biostatistics experts, Drs. Thisted and Ogenstad.

[3] UTC is happy to provide copies of Dr. Channick's report at the Court's discretion.

Respectfully submitted,



Michael J. Flynn (#5333)
Counsel for Plaintiff
United Therapeutics Corporation

cc: Clerk of the Court
All counsel of record

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	)	C.A. No. 23-975 (RGA) (SRF)

[PROPOSED] ORDER GRANTING PLAINTIFF UNITED THERAPEUTICS CORPORATION'S MOTION TO STRIKE EXPERT OPINIONS OF DR. NICHOLAS HILL AND STEPHAN OGENSTAD, PH.D.

Having considered Plaintiff United Therapeutics Corporation's ("UTC") Motion to Strike Expert Opinions of Dr. Nicholas Hill and Stephan Ogenstad, Ph.D., and the briefing and arguments presented by the parties,

IT IS HEREBY ORDERED this ___ day of _____, 2025, that:

1) UTC's Motion is GRANTED as to Dr. Hill. Paragraphs 16-17, 77-81, 94-96, 106, 110-112, and 148-179 of the Reply Expert Report of Dr. Nicholas Hill are struck and Dr. Hill is precluded from providing testimony at trial regarding any opinions set forth in those paragraphs.

2) UTC's Motion is GRANTED as to Dr. Ogenstad. Paragraphs 47-54 and 95-289 of the Reply Expert Report of Stephan Ogenstad, Ph.D. are struck and Dr. Ogenstad is precluded from providing testimony at trial regarding any opinions set forth in those paragraphs.

The Honorable Sherry R. Fallon
United States Magistrate Judge

EXHIBIT 1

ADD IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 23-975 (RGA) (SRF)

EXPERT REPORT OF DR. NICHOLAS HILL

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: the methods were not found to be obvious or anticipated by the prior art of record. The prior art does not teach or suggest the methods encompassing compounds substituted in the manner claimed by the Applicant.

VI. PRIOR PUBLIC USE (TYVASO)

131. It is my opinion that inhaled treprostinil has been widely and publicly used among the clinical community and our patients to improve exercise capacity in PH-ILD patients according to the approved dosing regimen for PAH in the Tyvaso label prior to April 17, 2019, thus rendering the '327 patent invalid. In my opinion, clinicians, including myself, were motivated to use Tyvaso for improving exercise capacity in PH-ILD patients as evidenced by the widespread off-label use of Tyvaso in these patients, as discussed below.

132. As explained further below, I have prescribed inhaled treprostinil to treat PH-ILD and am aware of colleagues who have prescribed inhaled treprostinil to treat their PH-ILD patients prior to April 17, 2020. Once a physician determines that a PH-ILD patient would benefit from inhaled treprostinil therapy, the patient and their guardians are informed of the nature of the treatment, the nature of their disease, and the treatment regimen in order to obtain consent. The nursing staff also would be informed of, if not already familiar with, the treatment regimen and the off-label indication. The patient would then bring the inhaled treprostinil medication and inhaler to their home and administer it according to the dosing regimen in the 2009 Tyvaso label, free for others to see.[115]

[115] As explained above in Section V.H, the Tyvaso labels from 2009 to 2021 disclose the same dosing regimen.

172. I also understand from counsel, as explained above in Section IV, that for an invention's public use to render a patent invalid, the publicly used invention must have been ready for patenting. An invention is ready for patenting if the claimed invention was reduced to practice. Here, the doctors were using Tyvaso off-label in PH-ILD patients according to the dosing regimen for PAH in the Tyvaso label. This dosing regimen falls within the claimed dosing regimen of claim 1. Moreover, as described above, physicians observed improvements in exercise capacity, NT-proBNP levels, and other quality of life measurements following treatment with Tyvaso. Because the doctors were already using the claimed method of treatment in practice and were seeing positive results, the invention was clearly ready for patenting. [redacted].[166]

173. Because the physicians' off-label use of Tyvaso to improve exercise capacity in PH-ILD patients was publicly accessible, discloses all limitations of claims 1-11, 15-19 of the '327 patent, and was ready for patenting, it is my opinion that this public use renders the '327 patent invalid.

VII. PRIOR PUBLIC SALE

174. Despite not being FDA-approved for the treatment of Group III patients, Tyvaso was nevertheless publicly available, prescribed, and sold for the treatment of patients with PH-ILD for years before the critical date of the '327 patent, April 17, 2019. Similarly, Tyvaso for the treatment of patients with PH-ILD was ready for patenting for several years before the critical date of the '327 patent.

[166] Waxman Dep. Tr. at 222:10-223:24; 231:1-6.

IX. UTC FAILED TO DISCLOSE MATERIAL REFERNCES TO THE USPTO

A. UTC Was Aware of the Size of the PH-ILD Patient Population and its Commercial Value

213. PAH occurs at a rate of approximately 2-5 in 100,000 people.[221] The prevalence of diagnosed and undiagnosed PH-ILD is estimated to range between 30,000 and 70,000 people in the United States.[222] I have reviewed a slideshow and transcript of a 2018 presentation by Dr. Aaron Waxman during UTC's Science Day on the findings of a study conducted by Dr. Mariana Faria-Urbina in 2018.[223] During his 2018 Science Day presentation, Dr. Waxman, speaking to the therapeutic opportunity for inhaled treprostinil, noted that "WHO Group III includes those patients with lung diseases of a number of different backgrounds[,] but that the focus of the presentation would be "on those patients who have probably the most prevalent diseases including chronic obstructive pulmonary disease, interstitial lung disease and a mix of the 2[,]" further noting that "[w]hen we think about the prevalence, its actually a ***huge medical problem*** out there."[224]

214. During the prosecution of the '327 patent from April 16, 2021 to November 28, 2023, UTC was well aware of the size and potential commercial value of the PH-ILD market. I have also reviewed the transcript of a 2017 presentation given by Dr. Waxman in which Dr. Waxman states, referring to Group 1 PH, that efforts to treat pulmonary vascular disease had "been focused on one ***very small subset*** of pulmonary vascular disease[,]" but that when other patients

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[221] GBD 2021 Pulmonary Arterial Hypertension Collaborators, *Global, regional, and national burden of pulmonary arterial hypertension, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021*, LANCET RESPIRATORY MED. (2024) at 5. This publication will be produced concurrently with this expert report.

[222] D.I. 55 (Decl. of Doug Kidder) at 10 (citing Liquidia Corporation's Form 10-K for 2022 (UTC_PH-ILD_002744)).

[223] A. Waxman, *The iTRE Study: Therapeutic Opportunity for Inhaled Treprostinil in Patients with PH Secondary to Primary Pulmonary Vascular Disease*, UTHR Science Day 2018 (2018) ("Waxman Presentation 2018") at Slides 11-16 (LIQ_PH-ILD_00101301); LIQ_PH-ILD_00140569 at -609.

[224] *Id*. (emphasis added).

with pulmonary vascular disease are considered, there was "a large number of potential patients[,]" as the treatment that had been directed at pulmonary vascular remodeling could "potentially benefit any patient with a form of pulmonary vascular disease[,]" including those classified as Group 3.[225] Dr. Waxman also noted that "if you don't get labels of what your're looking at, you wouldn't be able to discern one patient from another with pulmonary vascular disease."[226]

215. Dr. Waxman's 2017 remarks regarding the prevalence of WHO Group 1 PH as a "very small subset" of the total number of patients with a form of pulmonary vascular disease, and 2018 presentation describing the potential to treat WHO Group 3 patients, is consistent with my understanding of the disease landscape. In my opinion, Dr. Waxman's understanding is reflective of the knowledge of practicing physicians, who by 2017 would have been aware of the size and potential market for the treatment of patients with a form of pulmonary vascular disease other than Group 1 as the pathways that are active in patients with PAH are also active in patients with Group 3[.]"[227]

216. [redacted]

[225] 2017 Waxman JVMS Presentation (LIQ_PH-ILD_00147328) at 2:2-3:22 (emphasis added).
[226] *Id*.
[227] *Id*.
[228] UTC_WAT00628950-951
[229] *Id*.
[230] *Id*. (emphasis added).

217. In 2018, during an earnings call, Dr. Rothblatt, referring to PH-ILD patients, made the following statements to investors:

> In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved. So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.
>
> …
>
> [B]oth through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit [from Tyvaso and], there were unmistakable signals the some of the leading physicians in this field[,] I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works."[231]

218. In my opinion, Dr. Rothblatt's 2015 email to Roger Jeffs regarding her communication with Dr. Tapson as well as her 2018 statements made during UTC's earnings calls, are indicative of UTC's awareness surrounding the size and commercial value of the PH-ILD market and UTC's interaction with key opinion leaders, including Dr. Waxman. UTC was not only knowledgeable regarding the efficacy of Tyvaso and efforts by physicians and payors which "enable[d] some WHO Group III patients to benefit," but UTC itself, through its medical affairs group, had supported investigator-sponsored studies.[232]

[231] UTC 2018 Earnings Call (LIQ_PH-ILD_00000001) at -010.
[232] UTC_WAT00628950-951; UTC 2018 Earnings Call (LIQ_PH-ILD_00000001) at -010

219. In 2018, Dr. Rothblatt told investors that based on reported results, Tyvaso worked even better in PH-ILD patients than in those diagnosed with PAH.[233] Dr. Rothblatt's and UTC's awareness of the size and commercial value of the market for treating PH-ILD informed its later statements to shareholders in 2022 offering "greater assurance about the doubling of revenues by the end of '25" due to the uptake of Tyvaso DPI.[234] Similarly, in 2023, Dr. Rothblatt reported that Liquidia's Yutrepia, which at the time was set to be launched only for the treatment of PAH, would not challenge UTC's projected double-digit growth, noting that "there is so much robust room for growth and improvement in pulmonary hypertension[,]" which includes PH-ILD.[235]

220. In my opinion, Dr. Rothblatt's statements demonstrate knowledge of the potential market for PH-ILD and UTC's confidence that despite another product launching for the PAH indication, UTC would meet its revenue targets driven by the additional PH-ILD indication.

221. Therefore, it is my opinion that during the prosecution of the '327 patent, UTC was well aware of the size and potential commercial value of the PH-ILD patient population, and consequently the value of the patent protection provided by the '327 patent which is directed to a method of treating PH-ILD with inhaled treprostinil.

B. Stephen Maebius, Shaun Snader, and Peter Smith Had a Duty to Disclose Information to the USPTO

222. I understand from counsel that Stephen Maebius, Shaun Snader, and Peter Smith, all owed a duty of disclosure to the USPTO, which required that they disclose information, including references, to the USPTO material to the prosecution of the '327 patent. I also understand from counsel that this duty of disclosure existed from the time of patent application filing until the '327 patent issued.

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[233] LIQ_PH-ILD_00000001 at -004-007.
[234] LIQ_PH-ILD_00000013 at -018.
[235] *Id.* at -022.

1. Stephen Maebius

223. According to his CV, Mr. Maebius is a partner at Foley & Lardner LLP with over 30 years of experience.[236] Based on Mr. Maebius' CV, it is my understanding that Mr. Maebius "helps clients protect their innovation and transact business involving intellectual property assets."[237] Mr. Maebius' CV further indicates that prior to becoming a lawyer, he was a patent examiner in the Biotechnology Group of the USPTO.[238]

224. [redacted]

225. [redacted]

226. Mr. Maebius also acted as lead counsel during the '793 IPR.[241] Mr, Maebius was present at an oral hearing before the PTAB for the '793 IPR during which discussions took place regarding the admissibility and relevance of evidence from the District Court proceedings concerning the '793 patent.[242]

227. Thus, it is my opinion that during the prosecution of the '793 patent, Mr. Maebius was aware of the proceedings before the PTAB ('793 IPR) and the District Court proceedings

[236] Maebius Dep., Ex. 1.
[237] *Id*.
[238] *Id*.
[239] Maebius Dep. Tr. at 24:17-19, 43:17-46:17, 52:16-53:7.
[240] Power of Attorney (UTC_PH-ILD_009419 at -524); Snader Dep. Tr. at 67:18-69:18.
[241] May 13, 2022 PTAB Oral hearing (LIQ_PH-ILD_00101524 at -526).
[242] *Id.* at -526, -528-537, -549-552, -574-575, -602; UTC Press Release, July 24, 2023 (LIQ_PH-ILD_00101321).

regarding the '793 patent as evidenced by the fact that UTC submitted documents from the District Court proceedings during the '793 IPR.[243]

2. Shaun Snader

228. According to his LinkedIn profile, Shaun Snader is Vice President and Associate General Counsel (Intellectual Property) at UTC and is responsible for managing UTC's intellectual property portfolio, including supervising patent litigation for UTC.[244] I have reviewed the deposition transcript of Mr. Snader, in which Mr. Snader confirmed that he was "primarily responsible at United Therapeutics for the supervision and management of the patent prosecution that led to the issuance of the '793 patent[.]"[245]

229. During his deposition, Mr. Snader also confirmed that he signed the "Power of Attorney to Prosecute Applications Before the USPTO" on behalf of UTC, granting Stephen Maebius the power to prosecute the '327 patent application.[246]

230. [redacted]

231. [redacted]

[243] I submitted expert reports in both the '793 patent IPR and the earlier district court litigation between UTC and Liquidia regarding the '793 patent.
[244] Snader Dep., Ex. 2.
[245] Snader Dep. Tr. at 228:19-229:13.
[246] Power of Attorney (UTC_PH-ILD_009419 at -524); Snader Dep. Tr. at 68:2-69:18.
[247] *Id*. at 40:2-44:2.
[248] Maebius Dep. Tr. at 44:1-49:15.

[redacted]

232. [redacted]

233. It is my opinion that based on his position at UTC, his testimony during deposition describing his involvement in the '793 IPR, and his appearance in the Federal Circuit appeal of the District Court litigation concerning the '793 patent, Mr. Snader was aware of the proceedings before the PTAB, District Court, and the Federal Circuit concerning the '793 patent during the prosecution of the '327 patent.

234. [redacted]

235. It is my opinion that the February 12, 2024, letter to the FDA further evidences Mr. Snader's and UTC's knowledge of the materiality of the '793 patent for the prosecution of the '327 patent application.

[249] *Id*. at 102:21-103:4, 104:2-14, 104:22-105:15, 106:5-107:18, 140:13-141:10, 150:16-151:13.
[250] UTC Entry of Appearance, District Court Appeal (LIQ_PH-ILD_00101851); UTC Press Release August 31, 2022 (LIQ_PH-ILD_00101319); UTC Press release; July 24, 2023 (LIQ_PH-ILD_00101321).
[251] LIQ_PH-ILD_00000847; Snader Dep. Tr. 229:19-237:2.

3. Dr. Peter Smith

236. I understand, from reviewing his CV, that Dr. Peter Smith is UTC's Vice President of Product Development.[252] I also understand, from my review of the '327 patent cover page, that Dr. Smith is a named inventor of the '327 patent.

237. [redacted]

238. [redacted][254] [redacted][255]

239. [redacted]

[252] Smith Dep., Ex. 1.
[253] UTC_LIQ00104554; UTC_LIQ00104555; Smith Dep. Tr. at 185:4-186:15.
[254] UTC_LIQ00104555 at -556.
[255] *Id.*
[256] UTC_PH-ILD_081580 at -593; Smith Dep. Tr. at 157:24-159:24, 162:10-164:2.

240. [redacted]

241. It is my opinion that Dr. Smith, was familiar with Dr. Waxman's letter to the FDA, and the Agarwal 2015 reference during the prosecution of the '327 patent.

C. References Not Disclosed to USPTO

242. I am informed by counsel that certain references were not disclosed to the USPTO during the prosecution of the '327 patent. These references include: (1) the '793 Patent District Court Opinion, (2) my '793 Patent District Court trial testimony; (3) Federal Circuit affirmance of the '793 Patent District Court Opinion (including the Court's claim construction); (4) '793 IPR submissions. As described below, in my opinion, each of these references were material to the prosecution of the '327 patent, and therefore should have been disclosed to the USPTO during the prosecution of the '793 patent.

1. '793 Patent District Court Opinion and My Trial Testimony

243. Counsel has advised me that on June 4, 2020, before the '327 patent application was filed, UTC filed a complaint against Liquidia in the United States District Court for the District of Delaware.[258] UTC amended this complaint to further assert that Liquidia infringed its '793 patent on July 22, 2020.[259] I was an expert witness in this litigation and testified live at trial.

244. The Court's opinion in the District Court litigation includes its claim construction regarding the meaning of "pulmonary hypertension" in the '327 patent claims. The District Court

[257] Snader Dep. Tr. at 63:22-64:5.
[258] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 1 (D. Del. June 4, 2020).
[259] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 16 (D. Del. July 22, 2020).

concluded that based on the specification of the '793 patent, the scope of "treating pulmonary hypertension" in claim 1 includes "treating all five Groups of PH."[260]

245. I understand from counsel that the District Court trial concerning the '793 patent took place in March 2022 and the District Court issued its opinion in August 2022.[261] I further understand that the opinion was issued during the prosecution of the '327 patent application and prior to Mr. Maebius' amendment to the pending claims of the '327 patent covering interstitial lung disease.

246. As I mentioned, I testified during the '793 patent District Court litigation. I have reviewed the trial transcript containing my testimony where I testified regarding the meaning of "pulmonary hypertension" in the claims of the '793 patent. As I stated during trial, "'[p]ulmonary hypertension' as used, as far as I can tell in the patent, and would be used as a general term by a POSA comprises all the five different groups. It refers to . . . any condition where . . . there's an elevation of the pulmonary pressure, pulmonary pressures."[262]

247. This understanding of pulmonary hypertension is informed by column 1 line 41 of the '793 patent. As I stated during trial, "the first sentence says that pulmonary hypertension may occur due to various reasons, and the different entities of pulmonary hypertension were classified, based on clinical and pathological grounds, in five categories according to the latest WHO convention."[263]

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[260] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 1:20-cv-755-RGA-JLH, D.I. 433 at 38 (D. Del. Aug. 31, 2022) ("District Court Opinion"); *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464 (D. Del. 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023).
[261] *Id.*
[262] LIQ_PH-ILD_00101296 at -1298
[263] *Id.*

248. As I also previously testified, the pulmonary hypertension patients described in Example 1 of the '793 patent included patients in pulmonary hypertension Group 3, which includes patients with interstitial lung disease.[264]

249. It is my opinion, that given that the "treating pulmonary hypertension" term in the '793 patent claims was found to cover methods of treating all Groups of PH, including WHO Group 3 PH which includes interstitial lung disease, the proceedings before the District Court and its issued Opinion were material to the prosecution of the '327 patent claims which cover treating pulmonary hypertension associated with interstitial lung disease. Specifically, claim 1 was amended on May 10, 2023 during the prosecution of the '327 patent to read as indicated below:

> Claim 1: (Currently Amended) A method of improving exercise capacity in a patient having ~~treating a~~ pulmonary hypertension associated with interstitial lung disease ~~due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof~~, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease ~~a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof~~ an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises ~~an amount of~~ at least 6 micrograms per breath.[265]

250. Additionally, it is clear that Mr. Snader also believed that the '793 patent covers the same approved indication of treating PH-ILD which is covered by at least claim 1 of the '793 patent. I [redacted]

[redacted]

[redacted]

[264] *Id.*

[265] '327 patent file history at UTC_PH-ILD_009739.

[redacted][266]

[redacted][267]

251. I have been informed that the '793 patent was submitted to the USPTO during the '327 patent prosecution. [redacted].[268] I have reproduced claim 1 of the '793 patent below.

> A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.[269]

252. I have also been informed that neither the District Court's claim construction nor my trial testimony was submitted. In my opinion, these documents were material to the prosecution of the '327 patent claims and should have been submitted because they would have made clear to the Examiner that the method of treating pulmonary hypertension in the '793 patent covers the '327 patent claimed method of improving exercise capacity in PH-ILD as recited in claim 1 as indicated below. While Mr. Snader and Mr. Maebius submitted the '793 patent during

[266] LIQ_PH-ILD_00000847 at -852 (emphasis added); *see also* Snader Dep. Tr. at 229:19-237:2.
[267] Snader Dep. Tr. at 229:19-231:9.
[268] Maebius Dep. Tr. at 87:2-13.
[269] UTC_PH-ILD_009772 at -796 (claim 1).

prosecution, the District Court's claim construction and my testimony provided valuable context as to the scope and meaning of the '793 patent claims as encompassing treating PH-ILD patients that the USPTO did not have access to. In my opinion, had the USPTO been provided the District Court's claim construction and my trial testimony, that would form the basis to render at least claim 1 of the '327 patent unpatentable based on the '793 patent alone, or in combination with prior art cited by the USPTO during prosecution. For that reason, the District Court Opinion and my District Court Trial testimony are material references, which should have been disclosed to the USPTO during the prosecution of the '327 patent.

a. Claim 1 of '327 patent: "A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease"

253. As indicated above, the '793 patent was found to cover methods of treating all 5 PH groups. PH-ILD is a type of PH that falls within Group 3 PH and is therefore covered by the '793 patent's method of treatment. The fact that claim 1 of the '327 patent refers to a method of improving exercise capacity instead of a method of treatment, does not change my opinion. In my opinion, an improvement in exercise capacity, as reflected in for example an improvement in 6MWD, is clearly treating PH-ILD. An improvement in exercise capacity is something I routinely assess in my PH patients when determining whether a medication is effectively treating a patient. Moreover, to the extent UTC argues that the '793 patent is directed to hemodynamic changes that also does not change my opinion that the '793 patent covers the claimed method of improving exercise capacity in a patient having PH-ILD. This is because treprostinil is a vasodilator and its therapeutic effect is accomplished by favorable changes in a patient's hemodynamics. Therefore, in my experience, favorable hemodynamic changes in a PH patient generally correlate with improvements in exercise capacity.

b. Claim 1 of '327 patent: "comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath."

254. The claimed dosing regimen of inhaled treprostinil in the '327 patent is also encompassed within the '793 patent's dosing regimen. First, claim 1 of the '793 patent recites "administering by inhalation . . . a formulation comprising treprostinil." This disclosure of the use of inhaled treprostinil in '793 patent claim 1 and elsewhere in the specification encompasses the '327 patent claim 1's requirement for administering treprostinil by inhalation. Second, claim 1 of the '793 patent recites:

> a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.[270]

255. This dosing in the '793 patent overlaps with the '327 patent's claimed dosing. Both patents require that the effective dose of inhaled treprostinil is at least 15 micrograms provided in a single event dose. Additionally, the '327 patent requires that the single administration event comprise at least 6 micrograms per breath. This requirement is covered by the '793 patent claim's requirement that 15 micrograms can be delivered in 1 to 3 breaths. Obviously, the delivery of 15 micrograms in either 1 or 2 breaths would result in delivery of 15 or 7.5 micrograms per breath, respectively. Both of these amounts are at least 6 micrograms per breath as required by claim 1 of the '327 patent.

[270] UTC_PH-ILD_009772 at -796 (claim 1).

256. In my opinion, the '793 patent covers at least claim 1 of the '327 patent and therefore renders claim 1 of the '327 patent invalid. Accordingly, the '793 District Court Opinion on claim construction and my corresponding trial testimony were material to the prosecution of the '327 patent because they make clear, and I believe would have made clear to the '327 patent examiner, the scope of the '793 patent and that it would invalidate, alone or in combination with prior art cited during prosecution, of at least claim 1 of the '327 patent.

2. Federal Circuit Affirmance of the Claim Construction

257. I understand that on July 24, 2023, prior to the allowance of the '327 patent, the Federal Circuit affirmed the District Court's decision and agreed with me and the District Court that the '793 patent's claimed "'treating pulmonary hypertension' includes treating all five groups of pulmonary hypertension patients."[271] Neither Mr. Snader nor Mr. Maebius submitted the Federal Circuit's affirmance to the USPTO during prosecution of the '327 patent.

258. It is my opinion that both the District Court Opinion and the Federal Circuit's affirmance confirm that the claims of the '793 patent, including the mode of administration (inhalation), dosing, and number of breaths, and dose per breath, are utilized for all five PAH Groups, including patients with interstitial lung disease–the subject matter of the issued claims of the '327 patent.

259. Thus, it is my opinion that the Federal Circuit decision of July 24, 2023, which affirmed the District Court's claim construction that the '793 patent covers methods of treating all five PH Groups was material to the prosecution of the '327 patent and should have been submitted to the USPTO during the '327 patent prosecution for the same reasons provided for the '793 patent District Court opinion above.[272]

[271] *United Therapeutics Corp. v. Liquidia Tech. Inc.*, 74 F.4th 1360, 1368 (Fed. Cir. 2023).
[272] LIQ_PH-ILD_00101446.

3. '793 IPR Submissions and Federal Circuit's Invalidity Findings

260. I have reviewed UTC's Patent Owner Response, submitted in conjunction with the '793 IPR, in which UTC stated that "[t]he claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension."[273]

261. In its Patent Owner Response, UTC further described the invention in the '793 patent, stating that "[i]nhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease[,]" and that "[a]s of May 2006 – in fact, even as of January 28, 2021 – no therapies were approved for the treatment of pulmonary hypertension in patients with interstitial lung disease."[274]

262. I have reviewed portions of the'793 IPR Declaration of UTC's expert, Dr. Aaron Waxman filed in support of UTC's Patent Owner Response, in which he stated the following in a section of his declaration directed to unmet need in support patentability of the '793 patent:

> Inhaled treprostinil is also approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention[,]" and that "[a]t the time of the claimed invention and even as of today, there are no other therapies approved for the treatment of pulmonary hypertension in patients with interstitial lung disease.[275]

263. Both the Patent Owner Response and Dr. Waxman's supporting declaration sought to support the validity of the '793 patent by indicating that the treatment of PH-ILD covered an unmet need that was covered by the '793 patent. In my opinion, such an argument only makes sense if the claims of '793 patent include methods of treating PH-ILD – a fact which I testified to during my prior District Court testimony and which I continue to believe is true.

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[273] Patent Owner Response (LIQ_PH-ILD_00000110 at -180).
[274] *Id.* at -180-181.
[275] Waxman IPR Decl. (LIQ_PH-ILD_00102032) at ¶95-96.

264. I understand that the PTAB issued a Final Written Decision (FWD) invalidating the '793 patent on July 19, 2022, as obvious under 35 U.S.C. § 103. Thereafter, UTC filed a Notice of Appeal of the PTAB panel's FWD. On December 20, 2023, the Federal Circuit issued its opinion affirming the PTAB's decision finding the '793 patent invalid.[276]

265. I believe these references would have been material to the prosecution of the '327 patent because the arguments and opinions offered by UTC and Dr. Waxman in the POR and Waxman declaration, respectively, rely on the fact that the '793 patent claims cover methods of treating PH-ILD and specifically the FDA approved indication on the Tyvaso label. These references are therefore material to the prosecution of the '327 patent for all the same reasons discussed for the District Court Opinion above. These references provide valuable context, not only of the scope of the '793 patent claims, but also UTC's own affirmative positions that the claims of the '793 patent cover the same subject matter of the '327 patent. Thus, this information would permit the USPTO to reject the claims of the '327 patent based on the '793 patent alone or in combination with additional prior art because these statements would confirm the '793 patent's clam scope. Additionally, the PTAB's FWD is also material because it found all claims of the '793 patent invalid as obvious. Given that the '793 patent claim invalidates at least claim 1 of the '327 patent, either alone or in combination with additional prior art, in my opinion, the PTAB's finding that the '793 patent claims were obvious in view of the prior art runs contrary to the arguments in support of validity that Mr. Snader and Mr. Maebius made during the prosecution of the '327 patent. It specifically runs contrary to the arguments made during prosecution that the '327 patent with its much later filing date was non-obvious over the prior art.[277]

[276] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 2023-1805, 2023 WL 8794633 (Fed. Cir. Dec. 20, 2023).
[277] *See* Section V.I.

D. UTC's submission of these references in later filed patents further supports materiality of these references

266. U.S. Application Nos. 17/486,721 ("'721 application") and 17/707,651 ("'651 application"), like the '793 patent, are directed to a method of treating pulmonary hypertension by using an inhalation device comprising a formulation of treprostinil.[278] The '721 application and the application leading to the '793 patent are both continuations of U.S. App. No. 16/536,954, and the '651 application is a continuation of the '721 application.[279]

267. During the prosecution of the '721 and '651 applications, and before the notice of allowance was issued for the '327 patent, Mr. Maebius submitted numerous "Notification[s] of Related Proceedings" to the USPTO disclosing '793 IPR filings that contain allegations of unpatentability.[280] [redacted][281]

268. In my opinion, UTC's disclosure of allegations of unpatentability during the prosecution of the '721 and '651 applications and [redacted], further demonstrate the materiality of these allegations to the USPTO's patentability determination for all applications directed at related subject matter.

[278] *See* UTC_PH-ILD_009772 at -796 (claim 1); LIQ_PH-ILD_00147360; LIQ_PH-ILD_00147453.
[279] *See* UTC_PH-ILD_009772; LIQ_PH-ILD_00147377; LIQ_PH-ILD_00147455.
[280] *See, e.g.*, LIQ_PH-ILD_00147359 (UTC disclosing the Institution Decision for the '793 IPR, along with the Patent Owner's Preliminary Response to Petition and accompanying exhibits); LIQ_PH-ILD_00147437 (UTC disclosing the Petitioner's Reply and exhibits for the '793 IPR); LIQ_PH-ILD_00147452 (UTC disclosing Institution Decision for the '793 IPR, along with the Patent Owner's Preliminary Response to Petition and accompanying exhibits, Petitioner's Reply and exhibits, and Patent Owner's Sur-Reply and exhibits); LIQ_PH-ILD_00147486 (UTC disclosing the Final Written Decision for the '793 IPR)
[281] Maebius Dep. Tr. at 85:10-86:5.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: December 19, 2024

Dr. Nicholas Hill

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 23-975 (RGA)(SRF) **HIGHLY CONFIDENTIAL**

REPLY EXPERT REPORT OF DR. NICHOLAS HILL

inventor's knowledge was not scientifically certain and that other researchers helped them gain such scientific certainty. I have been informed that courts have held that researchers who have merely confirmed that an invention works to a scientific certainty were not co-inventors.

15. Additionally, I have been informed that in proving improper inventorship, an accused infringer may not necessarily have to prove the identity of the true inventor, it only has to prove that the named inventorship on the patent is incorrect.

C. Inequitable Conduct

16. My Opening Report set forth the legal standard section for inequitable conduct, which I incorporate herein by reference.[4] I note that Dr. Nathan's opinions are limited to the materiality of the references serving as the basis for Liquidia's inequitable conduct claims. Although Dr. Nathan provides the legal principles for the "intent" element of inequitable conduct, Dr. Nathan did not offer opinions with respect to intent.

17. In addition to providing his understanding of the "materiality" element of inequitable conduct, Dr. Nathan also opines on whether a reference is cumulative of information already before the examiner. Counsel has informed me that a reference is cumulative when it teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the examiner. I further understand from counsel that information from prior patent litigation proceedings is material.

III. PRIOR PUBLIC USE

A. Drs. Waxman, Tapson, Rajan Saggar, Rajeev Saggar, Channick, Parikh, and Nathan Treated PH-ILD Patients

18. Dr. Nathan asserts in his Rebuttal Report that the use of inhaled treprostinil to treat PH-ILD patients by Drs. Waxman, Tapson, Rajan Saggar, Rajeev Saggar, Channick, Parikh, and

[4] Hill Opening at Section IV.E.

I. The Prior Public Use Was Sufficiently Public

75. Dr. Nathan asserts that any off-label use of inhaled treprostinil for treatment of PH-ILD was not sufficiently public, relying on several flawed arguments.[162] I understand from counsel that for there to be prior public use, the public must be in possession of the claimed invention, which is satisfied if the public is informed of or can readily discern the claimed invention.

76. Dr. Nathan first argues that I have not identified any publications corroborating or disclosing the off-label use of Tyvaso by Drs. Tapson and Channick.[163] He claims that my opinions rely solely on Dr. Channick's declaration and that I do not provide any publications to support my assertion that these physicians publicly used Tyvaso off-label to improve exercise capacity in PH-ILD patients before April 17, 2019. A few paragraphs later, Dr. Nathan also argues that because I did not point "to any evidence that Dr. Tapson or Dr. Channick attempted to publish, present, patent, or commercialize the off-label use," the treatment was not publicly known.[164] This is clearly incorrect given the plethora of publications such as Agarwal 2015, 12th Annual John Vain Symposium, Faria-Urbina 2018 (all three authored or co-authored by Dr. Waxman), Parikh 2016 (co-authored by Dr. Tapson), Saggar 2009 and 2014 (authored by Drs. Rajeev Saggar and Rajan Saggar), and Dr. Rothblatt's 2018 investor statements (crediting Dr. Waxman). These examples further confirm that the practice of prescribing inhaled treprostinil for PH-ILD was well-known and not subject to secrecy as Dr. Nathan contends.

77. Next, Dr. Nathan contends that patients lacked the knowledge and skill to understand the claimed invention.[165] However, I understand from counsel that for prior public use

[162] *See* Nathan Rebuttal at ¶ 280.
[163] *See id.* at ¶ 279.
[164] *See id.* at ¶ 284.
[165] *See id.* at ¶ 281.

to apply, the public must be in possession of the claimed invention. This means that the public must be informed of or can readily discern the claimed invention. The fact that all the clinicians described in my Opening Report were prescribing Tyvaso to treat their patients with PH-ILD demonstrates that the prior public use was sufficiently public.[166] The patients knew they had PH-ILD, knew they were being prescribed Tyvaso to treat their PH-ILD, and reported back to their doctors and others on how it worked for them. These patients were not in a blinded clinical trial, subject to confidentiality, but were instead real-world patients. As explained in my Opening Report, patients are educated about their treatments, including at least the purpose, potential risks, expected benefits, and dosing regimen.[167] In clinical practice, physicians do not prescribe medications without explaining their use. If clinicians were prescribing inhaled treprostinil to PH-ILD patients, those patients necessarily would have been informed that the drug was intended to treat their PH-ILD. Furthermore, because Tyvaso was an FDA-approved drug when it was used off-label prior to April 2019, it was obtained through specialty pharmacies, which would send staff (typically nurses) to the PH-ILD patient's home to teach the patient how to administer the drug. If the patient visited the clinic, clinicians and doctors would explain the underlying PH-ILD condition and the treatment in detail such that the patient would understand the method of treatment and its rationale. Importantly, the specialty pharmacy staff would teach patients how to uptitrate their Tyvaso medication—this would educate patients about the Tyvaso dosing regimen such that they would be able to understand and discern the claimed method of treatment. This contradicts Dr. Nathan's assertion that such use of the claimed method of treatment would not have been understood by patients receiving the treatment.

[166] *See* Hill Opening at Sections VI.A-G.
[167] *See* Hill Opening at Section VI.A.

78. Then, Dr. Nathan argues that medical insurance providers would not have been in possession of the claimed invention because, according to him, patients who were purportedly treated off-label were represented to insurers as having PAH or PH out of proportion to their lung disease.[168] He further claims that I have provided no support for my assertion that clinicians "described PH-ILD patients as having out of proportion PH" for the purpose of securing insurance coverage.[169] However, as I explained above, Dr. Nathan's reliance on the "out of proportion" PH classification is incorrect and unsupported.[170] He assumed, without basis, that patients described in this manner were necessarily distinct from PH-ILD patients. Dr. Nathan's argument also overlooks the fact that insurance company representatives, many of whom are medical doctors, are well-informed about the diseases they cover or the therapies being prescribed. These representatives are often well-read on the relevant medical literature, treatment guidelines, and emerging uses of approved drugs. They understand what physicians are trying to accomplish when prescribing Tyvaso to PH-ILD patients and are aware of the clinical rationale behind such prescriptions. More specifically, medical insurance providers would have been aware of the TRIUMPH study, which was central in obtaining FDA approval for the PAH indication of Tyvaso, and would have understood the evidence gap when Tyvaso was then prescribed for PH-ILD patients. Furthermore, clinicians do not misrepresent the diseases or treatments when seeking insurance coverage. Dr. Nathan's opinion is also summarily dismissed because Dr. Rothblatt publicly stated that "payers" were paying for Tyvaso to treat PH-ILD.[171]

79. Further, Dr. Nathan again incorrectly relies on his theory that Tyvaso was not prescribed "for *PH-ILD* patients for the purpose or with the expectation of increasing exercise

[168] *See* Nathan Rebuttal at ¶ 283.
[169] *Id.*
[170] *See supra* Section III.A.
[171] LIQ_PH-ILD_00000001 (UTC 2018 Earnings Call Transcript) at -010.

capacity."[172] As discussed above, I have been informed by counsel that the prior public use inquiry does not include an intent requirement and it is thus my opinion that Dr. Nathan is improperly imputing the requirement that clinicians must have prescribed Tyvaso *with the intent* of improving exercise capacity in PH-ILD patients.[173] Further, Dr. Nathan's own recitation of the legal principles associated with prior public use do not include this requirement.[174] As I explained in my Opening Report, insurers were informed of, and could readily discern, the claimed features of the invention.[175]

80. Nonetheless, Dr. Rothblatt's 2018 statements dispense with Dr. Nathan's opinion.[176] This demonstrates that insurers were, in fact, reviewing and scrutinizing the reason for prescribing inhaled treprostinil in PH-ILD patients. Moreover, Dr. Rajan Saggar explicitly testified that [redacted][177] Despite these difficulties, Dr. Rajan Saggar [redacted].[178] Dr. Waxman testified that [redacted].[179] Dr. Tapson also testified that [redacted]e.[180] Moreover,

[172] *See* Nathan Rebuttal at ¶ 283.
[173] *See e.g., supra* ¶ 42.
[174] *See* Nathan Rebuttal at ¶¶ 27-32.
[175] *See* Hill Opening at ¶¶ 136, 139, 180, 183.
[176] *See* LIQ_PH-ILD_00000001 ("UTC 2018 Earnings Call") at LIQ_PH-ILD_00000010.
[177] *See* Rajan Saggar Sept. 17, 2024 Dep. Tr. at 172:20-173:17.
[178] *See id*. at 173:18-174:7.
[179] *See* Waxman Dep. Tr. at 67:12-68:10.
[180] *See* Tapson Dep. Tr. at 63:23-64:15.

Dr. Rothblatt told investors in 2018 that payors (insurance companies) were paying for Tyvaso to treat PH-ILD with improvements in exercise capacity.[181] This demonstrates that insurers were, in fact, reviewing and scrutinizing the reason for prescribing inhaled treprostinil in PH-ILD patients.

81. Third, Dr. Nathan argues that off-label prescribing was a private, risk-reward decision between patient and physician, asserting that the confidentiality of the patients' names and their respective medical treatment meant such use was not public.[182] However, Dr. Nathan provides no support for this claim other than his own assertion. There is nothing preventing the patient from discussing their treatment with the rest of the world since the patient is under no confidentiality obligation. And from the clinician's point of view, while individual patient names and individual patient data are certainly confidential, the fact that a population of PH-ILD patients were being treated with off-label Tyvaso is clearly not confidential. [redacted][183] If the information were as private as Dr. Nathan suggests, [redacted]. Moreover, as noted in the paragraph above, Dr. Martine Rothblatt, who is not even a medical doctor, knew PH-ILD patients were being treated with Tyvaso with the knowledge that their exercise capacity was improving and broadcasted that to the world in 2018.[184] And this prior public use was well documented and public, as presented in at least Agarwal 2015, Faria-Urbina 2018, and Dr. Waxman's 2017 presentation at the John Vain symposium, which was publicly available online as of March 2017.

[181] *See* LIQ_PH-ILD_00000001 (UTC 2018 Earnings Call) at -010.
[182] *See* Nathan Rebuttal at ¶ 284.
[183] Tapson Dep. Tr. at 43:8-45:14Rajeev Saggar Dep. Tr. at 224:16-226:8; Rajan Saggar Sept. 17, 2024 Dep. Tr. at 24:10-25:13; D.I. 54 (Channick Decl.) at ¶52; Channick Dep. Tr. at 35:7-17, 49:8-50:2, 144:20-147:13, 188:13-189:21.
[184] *See* LIQ_PH-ILD_00000001 (UTC 2018 Earnings Call) at -010.

Claims."[200] In Dr. Nathan's view, "no one had determined that the claimed method would achieve its intended purpose … until the INCREASE study results were unblinded … in February 2020."[201] Dr. Nathan is mistaken.

1. The claimed method was conceived and reduced to practice before April 2019

93. In support of his argument that the claimed method was neither conceived nor reduced to practice before April 2019, Dr. Nathan cites to deposition testimony from the three named inventors of the '327 patent stating that [redacted].[202] However, Dr. Nathan misses the point. It is irrelevant that [redacted].[203]

94. By stating in his reduction to practice analysis that nobody had "determined that the claimed method would work for its intended purpose until the results of the INCREASE study

[200] Nathan Rebuttal at ¶ 296.
[201] *Id.*
[202] *See* Nathan Rebuttal at ¶¶ 298-303.
[203] It is not surprising to me that these three UTC witnesses testified this way because [redacted] *See* Peterson Dep. Tr. at 33:16-25, 48:7-17; Deng Dep. Tr. at 15:11-16:1, 90:8-21; Smith Dep. Tr. at 22:3-12. Notably, Dr. Nathan does not cite to [redacted]

were unblinded in February 2020," Dr. Nathan is ignoring well-documents real world practice and instead arguing that a randomized clinical trial is necessary before an inventor can recognize whether a claimed method worked for its intended purpose or not.[204] However, I have been informed that showing that an invention will work for its intended purpose only requires a demonstration of the workability or utility of the claimed invention, and that this must show that the invention works for its intended purpose ***beyond a probability of failure*** but ***not beyond a possibility of failure***. Later refinements to and experiments with the invention do not preclude an earlier reduction to practice. The purpose of the INCREASE trial was to achieve FDA approval for UTC's Tyvaso and Tyvaso DPI products.[205] I have also been informed that courts have found the FDA's standard for drug approval to be a rigorous standard and that courts have found that the absence of FDA approval before the critical date does not prevent a finding of prior public use.[206] Thus, it is my opinion that the INCREASE trial was not necessary to show that the claimed method of treatment would work for its intended purpose and that the Prior Use Doctors reduced the claimed method to practice prior to April 2019.

95. Taking Dr. Waxman for example, [redacted].[207] [redacted].[208] [redacted]

[204] Nathan Rebuttal at ¶ 303.
[205] *See* Nathan Rebuttal at ¶ 679 ("UTC's products (Tyvaso or Tyvaso DPI for use in improving exercise capacity in PH-ILD patients) relied solely on the results of the INCREASE study to gain FDA approval for this indication.")
[206] *See supra* Section II.A.
[207] Waxman Dep. Tr. at 46:22-47:1, 49:22-50:5, 57:19-59:4, 93:15-94:8, 102:17-23.
[208] Waxman Dep. Tr. at 70:14-71:6, 91:6-94:8.

[redacted].[209] Here, Dr. Waxman clearly demonstrated, [redacted]

96. The other Prior Use Doctors have also testified or shown through their publications that they and their colleagues had treated PH-ILD patients with inhaled treprostinil to improve exercise capacity and had seen improvements prior to April 2019.[210] The other Prior Use Doctors have also demonstrated the workability or utility of the claimed method of treatment, and showed that the claimed method of treatment would work for its intended purpose beyond a probability of failure prior to April 2019. Thus, it is my opinion that the claimed method of treatment was conceived and reduced to practice prior to April 2019.

2. Dr. Nathan's "Numerous Prior Failed RCT's" Do Not Support That the Claimed Invention Was Not Reduced to Practice Until the INCREASE Study Results Were Known

97. Dr. Nathan cites to several presentations and emails from Liquidia and UTC that supposedly suggest that there was extensive negative literature regarding the treatment of PH-ILD

[209] LIQ_PH-ILD_00147328 (2017 Waxman Tr.) at 13:20-21 (emphasis added); *see also* UTC_PH-ILD_009828 (Agarwal 2015) (stating that "6MWD improved" in both restrictive and obstructive Group 3 PH patients and that the patients also reported "subjective improvement"), UTC_PH-ILD_009936 (Faria-Urbina 2018) at -936 ("From baseline to follow-up, we observed significant improvement in functional class … and 6-min walk distance" in "22 patients with PH associated with lung disease treated with inhaled treprostinil").
[210] *See supra* Sections III.A-G.

treprostinil to Group 3 patients was experimental and largely based on his experience with treating Group 1 patients, and thus merited further investigation."[230]

106. I have already addressed Dr. Nathan's arguments asserting that treatment of PH-ILD patients in Agarwal 2015 and Faria-Urbina 2018 were only hypothesis generating.[231] I have also explained in detail that Dr. Waxman would have determined that his method of treating PH-ILD patients would have worked for its intended purpose, and that the fact that there was further experimentation (*e.g.*, the INCREASE trial) after the public use does not prevent reduction to practice, especially in the context of clinical trials for the purpose of FDA approval.[232] I have also addressed Dr. Nathan's argument that the patient populations of Agarwal 2015 and Faria-Urbina 2018 are different from that of the INCREASE trial—the INCREASE trial allowed for patients with severe PH and indeed included many patients with such elevated PH.[233] For these reasons, it is my opinion that Dr. Waxman's deposition testimony demonstrates the reduction to practice of the claimed invention.

107. Dr. Nathan's argument that Dr. Waxman's prior use is only "hypothesis generating" is disingenuous and contradicts his own scientific publications. In a 2021 post-hoc analysis of the INCREASE study ("Lancet 2021"), Dr. Nathan stated that the INCREASE study results, "although intriguing and ***hypothesis generating***, ***warrants further validation in a prospective, randomised, placebo-controlled study***."[234] This is despite Dr. Nathan arguing throughout his Rebuttal Report that an RCT, such as the INCREASE trial, is "essential … to determine whether drugs are effective or not."[235] Regarding the INCREASE trial, Dr. Nathan characterized it as "the first time that a

[230] Nathan Rebuttal at ¶ 317-318.
[231] *See supra* Section III.L.5.
[232] *See supra* Sections III.A-B, L.1.
[233] *See supra* Sections III.A-B, L.1.
[234] LIQ_PH-ILD_00000216 (Lancet 2021) at -224 (emphasis added).
[235] *See e.g.* Nathan Rebuttal at ¶ 166 n.288.

7. The Claimed Improvements in FVC and Reductions in Exacerbations and Other Endpoints of the INCREASE Study Were Conceived and Reduced to Practice Before April 2019

109. Dr. Nathan argues that "there was significant uncertainty going into the phase III INCREASE study that PH-ILD patients would demonstrate improved exercise capacity following administration of inhaled treprostinil[.]"[239] I have already addressed Dr. Nathan's arguments regarding the alleged uncertainty surrounding the improvement in exercise capacity.[240]

110. Dr. Nathan also argues that there was significant uncertainty going into the phase III INCREASE study that PH-ILD patients would demonstrate improvements that comprise the limitations of the dependent claims.[241] First off, I understand that readiness for patenting can be shown by the invention (1) being reduced to practice or (2) being sufficiently disclosed in drawings or documents such that a POSA would have been enabled to practice the invention.[242] The invention of the '327 patent is essentially a dosing regimen for inhaled treprostinil used to improve exercise capacity in PH-ILD patients. This dosing regimen was both (1) reduced to practice and (2) sufficiently disclosed in drawings or documents to enable a POSA prior to April 2019. The dosing regimen was clearly disclosed in drawings or documents, such as in the 2009 Tyvaso Label, Agarwal 2015, Faria-Urbina 2018, and the 2017 INCREASE Study Description, prior to April 2019.[243] The dosing regimen was also reduced to practice, since the Prior Use Doctors used the dosing regimen in those drawing or documents to treat PH-ILD patients using inhaled treprostinil or their treatment of PH-ILD patients was reflected in those drawings or documents.[244]

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[239] Nathan Rebuttal at ¶ 327.
[240] *See supra* Section III.A-G.
[241] Nathan Rebuttal at ¶ 327.
[242] Hill Opening at Section IV.
[243] *See* UTC_PH-ILD_010692 (2009 Tyvaso Label) at -693; UTC_PH-ILD_009828 (Agarwal 2015); UTC_PH-ILD_009936 (Faria-Urbina 2018) at -937; LIQ_PH-ILD_00000185 (2017 INCREASE Study Description) at -194.
[244] *See supra* Sections III.A-F.

111. To the extent that Dr. Nathan argues that the dependent claims were not ready for patenting, I disagree. The dosing regimen was clearly reduced to practice or disclosed in a drawing or document such that it would enable a POSA. Tellingly, there would have been no extra step for a POSA to take, apart from practicing the same dosing regimen, in order to achieve the improvements in the dependent claim limitations, such as improvements in plasma concentration of NT-proBNP, exacerbations of lung disease, or FVC. A POSA would simply administer inhaled treprostinil, identical to how he would dose inhaled treprostinil to improve exercise capacity, and the effects described in the dependent claims of the '327 patent would flow from that same dosing regimen. To the extent that Dr. Nathan argues that the FVC improvement was unexpected, Dr. Nathan is attempting to read in an intent requirement that is not relevant to a prior public use inquiry.

8. The Claimed Invention Worked for its Intended Purpose of Improving Exercise Capacity in PH-ILD Patients Before April 2019

112. Dr. Nathan argues that the claimed invention did not work for its intended purpose prior to the unblinding of the INCREASE study results in February 2020 because the PH-ILD patients that the Prior Use Doctors treated had characteristics of PAH.[245] I have already addressed this argument above in at least Sections III.A-G. For the reasons discussed in those sections above, it is my opinion that the claimed invention worked for its intended purpose of improving exercise capacity in PH-ILD patients prior to April 2019.

[245] *See* Nathan Rebuttal at ¶¶ 334-335.

and Dr. Smith and Dr. Peterson did not begin until 2017.[337] To the extent that Dr. Nathan contends that [redacted]

VI. THE '327 PATENT IS UNENFORCEABLE DUE TO INEQUITABLE CONDUCT

148. My Opening Report explains the relevance and materiality of the information contained in (1) the Court's opinion in the previous District Court litigation, including its claim construction regarding the meaning of "pulmonary hypertension," (2) my District Court trial testimony, (3) the Federal Circuit's affirmance of the District Court's decision (numbers (1)-(3) collectively referred to as "District Court Documents"), (4) UTC's Patent Owner Response submitted in the '793 IPR ("'793 POR"), (5) the '793 IPR declaration of Dr. Aaron Waxman submitted in support of UTC's Patent Owner Response, (6) the PTAB's Final Written Decision ("FWD") invalidating the '793 patent, and (7) the Federal Circuit's opinion affirming the PTAB's FWD (numbers (4)-(7) collectively referred to as "'793 IPR Documents").[338] For the reasons set forth below, Dr. Nathan's analyses and conclusions regarding the cumulative nature and materiality of the undisclosed District Court Documents and '793 IPR Documents (collectively referred to as the "Undisclosed References") are incorrect.

A. The Undisclosed References Are Not Cumulative of Information Already Before the Examiner

149. Dr. Nathan incorrectly states that the "District Court Documents and the '739 IPR are substantively duplicative of materials already before the examiner" and that the "prosecution of the patent would have proceeded the same way whether the examiner had those documents or not."[339] As explained below, none of the materials already before the Examiner during the

[337] Deng Dep. Tr. at 15:11-20; Smith Dep. Tr. at 20:12-22:12; Peterson Dep. Tr. at 22:13-17.
[338] *See* Hill Opening at ¶¶ 242-265.
[339] Nathan Rebuttal at ¶ 884.

prosecution of the '327 patent are "substantively duplicative" of the Undisclosed References, nor do any of the materials already before the Examiner describe the scope of the '793 patent claims. As stated in my Opening Report, the Undisclosed References establish that the claims of the '793 patent cover the same PH-ILD subject matter as the claims of the '327 patent, which makes the Undisclosed References material.[340]

1. The District Court Documents Are Not Cumulative of the Documents Already Before the Examiner

150. Dr. Nathan argues that the District Court Documents are not material because they are cumulative of the documents already before the Examiner.[341] Specifically, Dr. Nathan states that the District Court Documents would not have been useful to the Examiner because "several sources" already before the Examiner, including Agarwal 2015, WO 2008/098196 ("Wade"), WO 2016/205202 ("Zhang"), and WO 2015/138423 ("Malinin"), explain that treprostinil could be used in connection with PH-ILD.[342] Dr. Nathan does not appreciate, or purposefully overlooks the materiality of the District Court Documents. In my opinion, the District Court Documents are not cumulative of information disclosed in Agarwal 2015, Wade, Zhang, or Malinin (collectively, the "Four Prior Art References"), nor do they provide the necessary context to understand the full scope of the '793 patent. In fact, Dr. Nathan's arguments about how a POSA would understand the scope of the '793 patent disclosure in the absence of the Undisclosed References runs directly contrary to positions Dr. Nathan and UTC are taking in the present litigation.

151. As I explained in my Opening Report, the District Court Documents confirm that the claims of the '793 patent cover treating patients with PH-ILD.[343] Dr. Nathan, however, argues

[340] *See* Hill Opening at ¶¶ 242-265.
[341] Nathan Rebuttal at ¶¶ 886, 890.
[342] *Id.* at ¶ 885.
[343] Hill Opening at ¶¶ 242-265.

that because Agarwal 2015 discloses "the use of treprostinil in connection with patients have 'restrictive' disease, [including] PH-ILD" and "an average increase in 6MWD from baseline to 6 months," the information contained in the District Court Documents is thereby "cumulative."[344] I disagree with Dr. Nathan's conclusion that Agarwal 2015 is cumulative to the District Court Documents because Agarwal 2015 does not disclose information pertaining to the scope of the '793 patent claims and the District Court Documents do.

152. As an initial matter, Dr. Nathan's reliance on Agarwal 2015 as cumulative to the District Court Documents is inconsistent with his own prior statements about the limitations of Agarwal 2015. Earlier in his report, Dr. Nathan states that Agarwal 2015 does not treat PH-ILD patients because the PH is "out of proportion" to ILD.[345] Thus, Dr. Nathan has taken the position that Agarwal 2015 is not directed to PH-ILD, which is consistent with his statements regarding Agarwal 2015 in the context of materiality for inequitable conduct. Thus, the District Court Documents are not cumulative to Agarwal 2015 based on Dr. Nathan's own opinion.

153. Dr. Nathan also explicitly points out other various alleged deficiencies in Agarwal 2015, including that it "does not disclose or calculate the dosage of treprostinil/breath[,]" does not separate the data for PH-ILD patients from other Group 3 PH patients, and lacks a "placebo group for comparison," which limits its predictive power.[346] He further argues that because the patient population in Agarwal 2015 included patients with obstructive, restrictive, and mixed obstructive/restrictive disease, it is impossible to determine what the effects of treprostinil treatment were specifically for PH-ILD.[347] Despite these criticisms, Dr. Nathan later relies on Agarwal 2015 to argue that it sufficiently describes the use of treprostinil in PH-ILD patients,

[344] Nathan Rebuttal at ¶ 885.
[345] *See id.* at ¶ 223.
[346] *Id.* at ¶ 165.
[347] *See id.* at ¶ 164.

making the District Court Documents cumulative.[348] He cannot have it both ways. If Agarwal 2015 lacks the necessary specificity and reliability to provide meaningful conclusions about treating PH-ILD patients, which I disagree with, then it also cannot serve as a basis for arguing that the District Court Documents are cumulative. In contrast, the District Court Documents make clear that the '793 patent claims cover treating patients with PH-ILD.[349] Agarwal 2015 does not discuss the scope of '793 patent.[350] Because Agarwal 2015 says nothing about the '793 patent, the District Court Documents provide new, material disclosures that are not cumulative of Agarwal 2015.

154. Dr. Nathan also argues that the District Court Documents are cumulative of the prior art documents—Wade, Zhang , and Malinin—cited by the Examiner in the March 6, 2023 rejection because, according to Dr. Nathan, they describe "'treat[ing]' PH-ILD with treprostinil."[351]

155. Dr. Nathan, citing my Opening Report for the proposition that Wade discloses the use of inhaled treprostinil for the treatment of PH-ILD, alleges that because the Examiner reviewed Wade and nevertheless permitted the '327 patent to issue, the District Court Documents are cumulative.[352] Dr. Nathan ignores what Mr. Maebius and Mr. Snader argued to the Examiner about Wade during prosecution.

156. As discussed in my Opening Report, during prosecution, Mr. Snader and Mr. Maebius argued that "Wade does not teach or suggest 'a single administration event that comprises

[348] *See id.* at ¶ 885.
[349] *See* Hill Opening at ¶¶ 243-259.
[350] *See id.* at ¶ 210.
[351] Nathan Rebuttal at ¶ 885 (citing UTC_PH-ILD_219604 (WO 2008/098196) at -607 ([0010]); UTC_PH-ILD_219854 (WO 2016/205202) at ¶ 99; UTC_PH-ILD_219746 (WO 2015/138423) at -780 ([00130])).
[352] Nathan Rebuttal at ¶ 885 (citing Hill Opening at ¶ 65).

at least 6 micrograms per breath' as amended claim 1 [of the '327 patent] recites."[353] Based on this argument, the Examiner allowed the '327 patent claims.[354] The '793 patent, on the other hand, discloses this limitation by describing delivering 15 mcg of treprostinil as a single administration event ("single event dose") in 1, 2, or 3 breaths.[355] And had the District Court Documents been submitted to the Examiner, the Examiner would have known that the '793 patent claims, which include PH-ILD patients, does disclose these very limitations Mr. Maebius and Mr. Snader alleged were lacking in Wade, thereby the District Court Documents are not cumulative to Wade.

157. Further, although Dr. Nathan argues that Wade makes the District Court Documents cumulative,[356] his own statements contradict this claim. Earlier in his report, Dr. Nathan criticizes Wade for failing to "demonstrate the intended or expected improvement of the Asserted Claims" because it "provides no data on the effects of inhaled Tyvaso on exercise capacity in patients with PH-ILD[.]"[357] But when discussing inequitable conduct, he relies on Wade as supposedly containing sufficient information to make the District Court Documents cumulative. In my opinion, Dr. Nathan and UTC cannot have it both ways—if Wade is insufficient to show efficacy in PH-ILD patients (which is odd because UTC filed a claim on this subject matter), then it cannot also serve as a basis for dismissing the materiality of the District Court Documents. Additionally, Wade does not provide any information about the scope of the '793 patent's claims, whereas the District Court Documents explicitly establish that the '793 patent covers treating PH-ILD patients. Accordingly, Wade does not render the District Court Documents cumulative.

[353] *See* UTC_PH-ILD_009419 (File History of '327 patent) at -9743; *see also* Hill Opening at ¶ 129.
[354] *See* UTC_PH-ILD_009419 (File History of '327 patent) at -9754.
[355] *See* UTC_PH-ILD_009772 ('793 patent) at claim 1.
[356] *See* Nathan Rebuttal at ¶ 885.
[357] *Id.* at ¶ 546.

158. During prosecution, Mr. Snader and Mr. Maebius argued that "[Zhang] teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath . . . [and that Zhang] teaches nothing regarding improving exercise capacity in any patient."[358] The District Court Documents establish the '793 patent discloses all these limitations. Specifically, because the District Court Documents confirm that the claims of the '793 patent include treating PH-ILD patients, they establish that the '793 patent and its claims disclose the alleged missing elements from Zhang, including treprostinil doses, inhaled treprostinil, and improvements in PH-ILD patients. The District Court Documents are not cumulative of the information disclosed in Zhang. Additionally, Zhang does not contain any information regarding the scope of the '793 patent's claims, whereas the District Court Documents do.

159. During prosecution, Mr. Snader and Mr. Maebius argued that "Malinin teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath."[359] For the reasons discussed above with respect to Zhang, the District Court Documents are not cumulative to Malinin. Additionally, like Wade and Zhang, Malinin does not contain any information regarding the scope of the '793 patent claims. Thus, the District Court Documents are not cumulative of the information disclosed in Malinin.

160. Further, and importantly, Dr. Nathan does not allege that the withheld '793 IPR Documents are cumulative to Agarwal 2015, Wade, Zhang, or Malinin. This omission is telling. The '793 IPR Documents confirm that UTC understood the '793 patent to encompass improving exercise capacity in PH-ILD patients—a key fact that was absent from any of the materials before the Examiner.

[358] UTC_PH-ILD_009419 (File History of '327 patent) at -9743.
[359] *Id*.

2. The '793 IPR Documents Are Not Cumulative of the Documents Already Before the Examiner

161. Dr. Nathan similarly argues that the '793 IPR Documents are cumulative of materials already before the Examiner, relying on the same reasoning he used to claim that the District Court Documents are cumulative.[360] In my opinion, the '793 IPR Documents are not cumulative of materials already before the Examiner.

162. In arguing that the '793 IPR Documents are cumulative of the '793 patent, Dr. Nathan states that it is "clear from the face of the '793 patent itself" that the '793 patent "cover[s] methods of treating PH-ILD."[361] However, as explained below, both UTC and Dr. Nathan have taken positions that directly contradict this point.[362]

163. Dr. Nathan argues that my analysis of claim 1 of the '793 patent is irrelevant to inequitable conduct but does not explain why beyond stating "for the reasons above."[363] It is unclear what "reasons above" Dr. Nathan refers to. Dr. Nathan also argues that my analysis of claim 1 of the '793 patent is incorrect, stating "a narrower claim with different elements is not necessarily anticipated or obvious because a separate patent claims a broader method of treatment."[364] Dr. Nathan's criticism is irrelevant because as explained below and in my Opening Report,[365] the '793 patent claims, as admitted by Mr. Maebius and Mr. Snader, cover all the elements of claim 1 of the '327 patent, including the improvement of exercise capacity in PH-ILD patients. This is confirmed by the '793 POR and Mr. Maebius' testimony [redacted]

[360] *See* Nathan Rebuttal at ¶ 888.
[361] *Id.* at ¶ 889.
[362] *See infra* Section VI.B.
[363] Nathan Rebuttal at ¶ 891.
[364] *Id.*
[365] Hill Opening at ¶¶ 253-256.

[redacted].[366] It is also confirmed by the [redacted].[367]

164. Dr. Nathan also argues that the treatment described in the '793 patent is defined as an improvement in hemodynamics, whereas claim 1 of the '327 patent requires an improvement in exercise capacity.[368] He contends that these concepts are distinct and that my analysis of the '793 patent improperly disregards this distinction.[369] I disagree because, as confirmed [redacted].[370] Specifically, in the '793 POR, Mr. Maebius and Mr. Snader argued that the claims of the '793 patent satisfied a long-felt but unmet need for this exact indication by stating that "[i]nhaled treprostinil is currently approved for [PAH] and [PH-ILD]."[371] To make this argument, [redacted].[372] When asked about this statement in the '793 POR, Mr. Maebius confirmed that it would inform the Examiner that the '793 patent claims cover the PH-ILD indication on the Tyvaso label, which specifically states: "Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability."[373] These representations leave no

[366] *See* '793 POR (LIQ_PH-ILD_00000110) at -180-181; Maebius Dep. Tr. at 43:17-46:17, 137:3-18.
[367] *See* LIQ_PH-ILD_00000847 ([redacted]) at -852; Snader Dep. Tr. at 229:19-237:19.
[368] Nathan Rebuttal at ¶ 892.
[369] *Id*.
[370] *See* Maebius Dep. Tr. at 136:1-137:18.
[371] *See* '793 POR (LIQ_PH-ILD_00000110) at -180.
[372] *See* Maebius Dep. Tr. at 137:3-18.
[373] *See id.* at 137:3-18; UTC_PH-ILD_010744 (Tyvaso 2021 label) at -745.

doubt that Mr. Maebius and Mr. Snader argued that a POSA would understand that the '793 patent claims cover improving exercise capacity in PH-ILD patients.[374] Dr. Nathan's current position directly contradicts the arguments that Mr. Maebius and Mr. Snader advanced in the '793 IPR, where they relied on this very interpretation of the '793 patent to support its validity.

165. On the issue of hemodynamics, Dr. Nathan's cites to riociguat's failure in the RISE-IIP trial as a "practical example" that hemodynamic effects do not always produce a "therapeutic or functional effect."[375] I disagree that Dr. Nathan's analogy to riociguat is relevant to the issue here, particularly given that riociguat and treprostinil are two very different drugs. In fact, the riociguat trial was stopped due to safety concerns rather than for a lack of perceived improvements in hemodynamics and therapeutic effects. Importantly, this is not about whether every PH drug improves exercise capacity—it is about whether the Examiner was deprived of material information that affected their analysis of the '327 patent's claims.

166. For the purposes of arguing a lack of materiality, Dr. Nathan now admits that the '793 patent covers a method of treating patients with PH-ILD, stating that this is "clear from the face of the '793 patent itself."[376] However, in both his declaration in support of UTC's preliminary injunction ("PI Declaration") and in his Rebuttal Report, he argues that the '793 patent does not disclose a method of improving exercise capacity in PH-ILD patients.[377] Dr. Nathan's opinion completely undercuts his argument that the '793 IPR Documents are cumulative to the '793 patent

[374] Further reinforcing this position, UTC, [redacted] *i.e.*, PH-ILD. *See* LIQ_PH-ILD_00000847 ([redacted]) at -852.
[375] Nathan Rebuttal at ¶ 892.
[376] *Id.* at ¶ 889.
[377] *See* D.I. 28 (Nathan PI Decl.) at ¶ 176; Nathan Rebuttal at ¶ 553; *see also* Nathan PI Dep. Tr. at 250:23-254:25.

itself. That Dr. Nathan is willing to take such inconsistent positions underscores how material the '793 IPR Documents are.

167. Dr. Nathan also asserts that the dosing limitations in claim 1 of '327 patent—the requirement to titrate up to a "maximum tolerated dose"—distinguish it from the '793 patent, which does not explicitly contain this limitation.[378] I do not agree with Dr. Nathan's reasoning. Dr. Nathan appears to be taking the position that for information to be material, it must be material to every limitation of a claim. However, I understand from counsel that is information is material if the information itself, or combined with other information, impacts the patentability of a claimed invention.

168. Nonetheless, in my opinion, Dr. Nathan is misreading claim 1. Specifically, claim 1 of the '327 patent does not require that that the dose be titrated up to a maximum tolerated dose. Rather claim 1 merely provides that a range of doses between 15 ug "up to" a maximum tolerated dose may be used, not that a maximum tolerated dose must be attained.[379] The dosing range in claim 1 of the '793 patent of 15-90 ug clearly overlaps with the claimed range in the '327 patent.[380] Furthermore, the '793 patent claims disclose dosing between 15-90 ug in 1 to 3 breaths, which involves dose adjustments to achieve the specified range.[381] This is dose titration.

169. Dr. Nathan also argues that because Liquidia's petition for IPR was before the Examiner, "by definition, the Final Written Decision is substantively duplicative."[382] This argument is flawed. Dr. Nathan appears to argue that by disclosing a select document from the IPR, the Examiner would somehow have knowledge of other relevant documents in the IPR. I do

[378] Nathan Rebuttal at ¶ 892.
[379] *See* '327 patent at claim 1.
[380] *See* UTC_PH-ILD_009772 ('793 patent) at claim 1.
[381] *See id*.
[382] Nathan Rebuttal at ¶ 893.

not understand how that would be possible. The positions taken in an IPR petition represent the arguments of the challenging party, not a determination of the claims' actual scope. And importantly, the IPR petition does not include Mr. Snader's and Mr. Maebius' statements refuting the petition. In contrast, the Final Written Decision reflects the PTAB's independent analysis and ultimate ruling on the scope of the '793 patent claims. Even in the abstract, it does not make sense that a single document from one party to an IPR would be cumulative of either argument made in an opposing party's submission and arguments and rationale set-forth by the PTAB in its FWD. The Examiner was entitled to consider not just Liquidia's arguments, but also the PTAB's findings. Thus, the Final Written Decision is not cumulative of Liquidia's IPR petition but instead provides material conclusions that the Examiner never had an opportunity to review.

170. I also understand that UTC has argued the Undisclosed Documents are cumulative to the '793 patent because the specification of the '327 patent incorporates the '793 patent by reference.[383] I have reviewed this portion of the '327 patent's specification and disagree. Particularly, the '327 patent only references the '793 patent in the context of disclosing a type of inhalation delivery device. Specifically, the specification states: "Pulsed inhalation devices are disclosed, for example, in U.S. patent application publication No. 20080200449, U.S. Pat. Nos. 9,358,240; 9,339,507; 10,376,525; and 10,716,793, each of which is incorporated herein by reference in its entirety."[384] Thus, UTC's argument that the incorporation by reference of the '793 patent renders the Undisclosed References cumulative is misleading. In fact, rather than supporting UTC's position, this selective reference underscores the materiality of the Undisclosed References, as the '793 patent was only mentioned in the '327 patent in the context of pulsed

[383] *See* D.I. 239 at 1. Dr. Nathan does not appear to make this argument. I include it here in the event Dr. Nathan does raise it at trial even though it is not in his report.
[384] '327 patent at 20:53-57.

inhalation devices and not for the fact that the '793 patent and its claims are directed to the same subject matter as the '327 patent claims.

B. Inconsistent Positions Taken by Dr. Nathan and UTC Further Support That the Undisclosed References are Material

171. Dr. Nathan's and UTC's inconsistent positions concerning how a POSA would understand the disclosure and claims of the '793 patent further establish why the Undisclosed Documents are material to the prosecution of the '327 patent.

172. Dr. Nathan has expressly contended that the '793 patent itself is not cumulative to the claims of the '327 patent. For instance, in support of UTC's preliminary injunction motion, Dr. Nathan argued:

- "A POSA would not understand the '793 patent to teach the administration of treprostinil to improve exercise capacity in a patient having PH-ILD[.]"[385]
- "[T]he '793 patent does not teach anything about what the '327 patent has as its claim in terms of improving exercise tolerance, FVC and other things that are within the -327 claim."[386]

173. In Dr. Nathan's Rebuttal Report, he argues that the "'793 patent does not disclose a method of improving exercise capacity in a patient having PH-ILD," nor does it "discuss improvements in exercise capacity."[387] Dr. Nathan also states that neither Examples 1 nor 2 of the '793 patent "disclose improvement in exercise capacity, nor is it clear whether any of the patients treated in either Example suffered from PH-ILD."[388] Dr. Nathan concludes that in his opinion, the

[385] D.I. 28 (Nathan PI Decl.) at ¶ 176.
[386] Nathan PI Dep. Tr. at 250:23-251:4.
[387] Nathan Rebuttal at ¶ 553. In the context of inequitable conduct, Dr. Nathan contradicts his earlier positions by stating that "[t]he term 'pulmonary hypertension,' as defined by the '793 patent, includes all 5 [PH] groups[,]" and cites the '793 patent itself, along with two of the District Court Documents. *Id.* at ¶ 886. Notably, Dr. Nathan's reliance on these documents underscores that they are not cumulative, but essential to properly interpreting the full scope of the '793 patent.
[388] *Id.* at ¶ 553.

"'793 patent does not disclose 'a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.'"[389]

174. During the preliminary injunction stage, counsel for UTC also argued that a POSA would not understand the specification and claims of the '793 patent to teach anything relevant to the '327 patent. Specifically, counsel for UTC stated that the '793 patent teaches the treatment of a "different patient class" than the '327 patent and that "there is nothing in the '793 patent whatsoever about exercise capacity, period, full stop. The words just don't even appear in there."[390] In other words, UTC has taken the position that the '793 patent and its claims are ***not*** directed to PH-ILD patients, but instead a "different patient class," and ***not*** directed to improving the exercise capacity of PH-ILD patients.

175. During the course of this litigation, UTC asserted in a response to a discovery question that "'793 patent claims do not express specific preferences for treating PH-ILD."[391]

176. In summary, both Dr. Nathan and UTC have taken the position that a POSA would understand the '793 patent: ***fails*** to disclose patients with PH-ILD (it discloses a "different patient class"); ***fails*** to disclose "administration of treprostinil to improve exercise capacity in a patient having PH-ILD"; ***fails*** to disclose claims directed to PH-ILD; and ***fails*** to disclose "a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease." If Dr. Nathan and UTC are correct (which I disagree with), then the Examiner, purportedly considering the '793 patent from the perspective of a POSA, would reach the same conclusion during prosecution of the '327 patent.

[389] *Id.* at ¶ 555.
[390] April 23, 2024 Hearing Tr. at 24:2-25, 66:5-8.
[391] UTC Amended First Supplemental Response to Interrogatory No. 1 at 26.

177. This alleged POSA's view of the claims and disclosure of the '793 patent is, however, in direct contradiction to express statements Mr. Maebius and Mr. Snader made with respect to the '793 patent claims in the Undisclosed Documents, making these documents material, not cumulative. Specifically, as explained above, [redacted].[392]

178. If, as UTC and Dr. Nathan have argued, the '793 patent was insufficient to inform a POSA that it covered PH-ILD treatment and improvements in exercise capacity, then the Examiner could not have properly assessed its relevance to the claims of the '327 patent without additional context. The Undisclosed References fill this gap by confirming that UTC itself previously acknowledged the '793 patent's applicability to PH-ILD, a fact that directly contradicts its litigation positions and underscores the materiality of these documents.

179. To the extent Dr. Nathan argues that I did not explain why the Examiner would have applied a different definition of pulmonary hypertension or what that different definition could have been, his argument is flawed for various reasons. Firstly, the Examiner never relied on the '793 patent to reject the '327 patent's claims, and thus, the Examiner belief's regarding the scope of the '793 patent remain unclear. Next, as discussed in my Opening Report, the District Court Documents explicitly define "pulmonary hypertension" as stated in the '793 patent as including PH-ILD.[393] This directly contradicts UTC's positions as explained above.[394] Had the Examiner reviewed these District Court Documents, they would have understood that the '793 patent was material to the '327 patent. Lastly, given that the District Court Documents provide

[392] *See supra* ¶ 156; *see also* Maebius Dep. Tr. at 137:3-18.
[393] Hill Opening at ¶¶ 242-265.
[394] *See supra* Section VI.

details regarding the scope of the '793 patent that were not readily apparent from the prior art already before the Examiner, they cannot, by definition, be "cumulative" of information that was already considered.

VII. RESERVATION OF RIGHTS

180. This report is based on information currently available to me. I reserve the right to continue, update, and expand my investigation and analysis in a supplemental report if additional documents, deposition transcripts, or any other information is produced by UTC. I reserve the right to respond to any matters raised by UTC, or any opinions or conclusions of any expert, by relying on documents or other information that is additional to the information considered and cited herein. I further reserve the right to prepare exhibits to summarize and demonstrate my testimony at trial, and to supplement my opinions as permitted by any Court order.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: February 20, 2025

Dr. Nicholas Hill

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

Case No. 23-975-RGA-SRF

UNITED THERAPEUTICS CORPORATION,

Plaintiff

vs.

LIQUIDIA TECHNOLOGIES, INC., and

Defendants

* * [redacted] * *

VIDEOTAPED DEPOSITION OF

NICHOLAS HILL, M.D.

WEDNESDAY, MARCH 12, 2025

8:32 a.m. - 5:29 p.m.

Reported by: Sandra A. Deschaine, CSR, RPR, CLR, CRA

Job No.: 10330

sale --

MR. SUKDUANG: You could read that section --

BY MR. JACKSON:

Q. -- in terms of how you were applying it in your opinion -- or in your report?

MR. SUKDUANG: You can read your report.

And object to the extent it calls for a legal response.

(Witness reviewing document.)

A. It appears that as -- you know, my understanding from counsel is that the section Prior Sale adds some conditions for, you know, how to establish prior sale. But I think it is the case that the prior public use encompasses a certain language that would be relevant to prior sale.

BY MR. JACKSON:

Q. Okay. So when you were applying and analyzing whether something was prior public use, you analyzed whether it was commercially exploited, correct?

A. That would be part of establishing

that.

Q. Yeah. And is it your understanding when you were doing that that prior sale was a subset of that?

MR. SUKDUANG: Objection, mischaracterizes the report.

A. I think there's clearly overlap between both of them, so I see them as conjoint.

Q. In paragraph 27, you also mention whether the claim was -- the claimed invention was reduced to practice.

Do you see that?

A. I do.

Q. Did you have any -- do you have any -- were you provided any opinions or direction about what it meant to be reduced to practice?

MR. SUKDUANG: You can answer that "yes" or "no."

A. Yes.

BY MR. JACKSON:

Q. Okay. And so what is it -- so in terms of you providing your opinions in this report, what did you -- what was the

principle you used for whether something was reduced to practice?

MR. SUKDUANG: And objection, in the sense it calls for a legal conclusion.

You can answer that in your personal capacity, or your understanding, I should say.

A. It means that practitioners of the art brought it into their practice and applied it.

BY MR. JACKSON:

Q. For purposes of analyzing whether something was reduced to practice, did you consider whether or not the invention would work for its intended purpose?

MR. SUKDUANG: Objection to the extent it calls for a legal conclusion.

You can answer that to your understanding.

A. Could you repeat that question, please?

BY MR. JACKSON:

Q. Sure. For the purposes of analyzing whether something was reduced to

practice -- let me strike that. Strike that.

You analyzed whether the invention here was reduced to practice, right?

A. Yes.

Q. For the purposes of conducting that analysis, did you consider whether the invention would work for its intended purpose?

MR. SUKDUANG: Objection to the extent it calls for a legal conclusion.

You can answer that to your understanding.

A. That would be part of my analysis, yes.

BY MR. JACKSON:

Q. And so the analyses you performed would be you analyzed whether or not, in fact, it worked for its intended purpose to determine whether or not it had been reduced to practice; is that right?

MR. SUKDUANG: Asked and answered.

A. I think so.

BY MR. JACKSON:

Q. The -- at anywhere in this

report -- strike that.

Let's just look at paragraph 35.

MR. SUKDUANG: 35?

MR. JACKSON: Yes.

BY MR. JACKSON:

Q. The first sentence reads, "I've been informed by counsel that an inventor does not need to know, however, that an invention will work for its intended purpose in order for a conception to be complete."

Did I read that right?

A. You did.

Q. So that uses the words "intended purpose."

Do you see that?

A. Yes.

Q. Anywhere else in this report do you use the words "intended purpose"?

MR. SUKDUANG: Why don't you take the time to read your entire report to provide that answer to Mr. Jackson?

A. I don't know with certainty.

BY MR. JACKSON:

Q. Okay. Let's go to your Reply Report for a second. Paragraph 4, you

Reply Report. The last sentence -- or the last two sentences read, "Counsel has informed me that a reference is cumulative when it teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the examiner. I further understand from counsel that information from prior patent litigation proceedings is material."

Did I read those two sentences right?

A. Did you say paragraph 17?

Q. Yes, of your Reply Report.

MR. SUKDUANG: You're in the wrong --

BY MR. JACKSON:

Q. And I'll do it -- I'll do it again, and I'll do it one by one.

Paragraph 17, the second sentence.

Are you with me?

A. Yes.

Q. Reads, "Counsel has informed me that a reference is cumulative when it teaches no more than what a reasonable examiner would consider to be taught by the

prior art already before the examiner."

Did I read that right?

A. Yes.

Q. Did you do any analysis of whether or not the material you focused on for purposes of inequitable conduct was cumulative in your Opening Report?

MR. SUKDUANG: Objection to the extent it calls for a legal response.

You can answer to your understanding.

A. I believe I did.

BY MR. JACKSON:

Q. Can you show me where the word "cumulative" appears anywhere in your Opening Report?

MR. SUKDUANG: You can go read your Opening Report, and because Mr. Jackson has asked you to do that, to identify the word "cumulative," or he can rephrase the question.

A. I think -- I can save us some time. The term "cumulative" does not appear in my original report.

BY MR. JACKSON:

EXHIBIT 4

From: Pappas, Katherine
To: z/Liquidia v UTC 308970-201
Cc: UTCvLiquidia-Del-23cv975; DG-ILD
Subject: UTC v. Liquidia (23-975) - FDA submissions and correspondence
Date: Wednesday, April 9, 2025 8:11:30 PM

EXTERNAL
Counsel,

This Hatch-Waxman litigation focuses on Liquidia's Yutrepia NDA, which is why UTC served RFP Nos. 1 and 2 seeking production of Liquidia's Yutrepia NDA, all amendments or supplements, and all correspondence with FDA regarding the same. In response to UTC's RFP Nos. 1 and 2, Liquidia agreed to produce its Yutrepia submissions and correspondence with FDA regarding Liquidia's Yutrepia NDA on a rolling basis, which Liquidia reaffirmed during the parties' Oct. 1, 2024 and Oct. 23, 2024 meet-and-confers and by email on Oct. 8, 2024. On Friday, March 28th, Liquidia issued a press release that refers to FDA action relating to a "resubmission that [Liquidia] filed on Monday." This press release also states that "FDA confirmed that the resubmission was a complete, Class 1 response to the previous action letter[.]" However, Liquidia has not apparently produced any correspondence with (or submissions to) FDA dated from 2025, and certainly not from within the last month.

To the extent that Liquidia contends it has already produced the FDA submission that Liquidia "filed on Monday" as well as the correspondence from FDA "confirm[ing] that the resubmission was a complete, Class 1 response to the previous action letter," referenced in the press release, please provide the corresponding BATES numbers. Regardless, immediately produce all unproduced FDA submissions and correspondence regarding Liquidia's Yutrepia NDA.

Regards,

KATHY PAPPAS
Associate
McDermott Will & Emery LLP 12636 High Bluff Drive, Suite 325, San Diego, CA 92130
Tel +1 619 467 1806 **Email** kpappas@mwe.com
Website | **vCard** | **LinkedIn**

EXHIBIT 5

From: Preston, Rachel L
To: Adykhuis@mwe.com; Upton, Rozzi D; mflynn@morrisnichols.com; McDermott, Sydney; kpappas@mwe.com; jvallen@mwe.com; aburrowbridge@mwe.com; Dcarsten@mwe.com; Jackson, William C
Cc: DG-ILD; z/Liquidia v UTC 308970-201; UTCvLiquidia-Del-23cv975; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Subject: RE: UTC v. Liquidia (23-975) Nov. 13 M&C
Date: Friday, November 15, 2024 11:54:46 AM

EXTERNAL
Counsel,

As we discussed and then requested in our 11/13 email, please indicate your position with respect to Liquidia's proposed extension by noon Monday 11/18. Liquidia maintains that a one-month extension of expert discovery is warranted given the significant ongoing fact discovery in this case, including the discovery disputes pending before the Court and the deposition of Aaron Waxman, which is scheduled for the day before expert reports are due.

As we previously indicated, if UTC agrees to these proposed extensions, Liquidia will not further seek the deposition of Dr. Rothblatt in this case. If UTC will not agree, please provide your availability for a Court hearing teleconference between and including Nov. 21-26.

Regards,
Rachel

From: Dykhuis, Art <Adykhuis@mwe.com>
Sent: Thursday, November 14, 2024 1:43 AM
To: Upton, Rozzi D <rupton@cooley.com>; Preston, Rachel L <RPreston@cooley.com>; mflynn@morrisnichols.com; McDermott, Sydney <Smcdermott@mwe.com>; Pappas, Katherine <Kpappas@mwe.com>; Vallen, Jake <Jvallen@mwe.com>; Burrowbridge, Adam <Aburrowbridge@mwe.com>; Carsten, Douglas <Dcarsten@mwe.com>; WJackson@goodwinlaw.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; Karen Keller <kkeller@shawkeller.com>; nhoeschen@shawkeller.com
Subject: Re: UTC v. Liquidia (23-975) Nov. 13 M&C

[External]

Rozzi, as an update, we are still working on UTC's responsive email regarding the issues discussed on the meet and confer earlier today and we will respond further when able.

Thanks,

Art

From: Upton, Rozzi D <rupton@cooley.com>

Date: Wednesday, November 13, 2024 at 1:12 PM
To: Preston, Rachel L <RPreston@cooley.com>, mflynn@morrisnichols.com <mflynn@morrisnichols.com>, Dykhuis, Art <Adykhuis@mwe.com>, McDermott, Sydney <Smcdermott@mwe.com>, Pappas, Katherine <Kpappas@mwe.com>, Vallen, Jake <Jvallen@mwe.com>, Burrowbridge, Adam <Aburrowbridge@mwe.com>, Carsten, Douglas <Dcarsten@mwe.com>, WJackson@goodwinlaw.com <WJackson@goodwinlaw.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>, z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>, UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>, Karen Keller <kkeller@shawkeller.com>, nhoeschen@shawkeller.com <nhoeschen@shawkeller.com>
Subject: RE: UTC v. Liquidia (23-975) Nov. 13 M&C

[External Email]
Hi Art,

Further to our discussion, we will look for your responses on the two discovery issues that Liquidia otherwise intends to raise with the Court tomorrow.

1. **De-designation of the deposition transcripts of Faria-Urbina and Rajan Saggar.** We understand you will respond this evening regarding de-designation and agreement for Russell Schundler to view these transcripts to the extent you maintain any of the information is Confidential under the Protective Order. We will consider such a proposal in potentially avoiding an issue for the Court to consider. [redacted] We will look for your response later today.

2. **Production of documents and communications, as indicated in the October 18 email from John Habibi.** As discussed, Liquidia's position is that, given deposition testimony in this case and productions from third party witness, Rajan Saggar, UTC's search and production to-date are clearly inadequate. We seek a further targeted search for these communications to include email of the additional UTC employees identified in John Habibi's email of October 18 (attached). [redacted] We will look for your response later today.

Also, as we discussed, and in view of the significant ongoing fact discovery in this case (including but not

limited to the deposition of Aaron Waxman scheduled to occur one day before opening expert reports are currently due), we propose the following one month extension of expert discovery deadlines which can be accommodated within the current trial date. As we indicated, if UTC agrees to these proposed extensions, Liquidia will not further seek the deposition of Dr. Rothblatt in this case. We believe that Judge Fallon's decision to deny the deposition (without prejudice) was incorrect in light of information and testimony that has come to light after the parties submitted their briefing on this issue. Please indicate your position with respect to the proposed extensions this week.

	Scheduling Order (DI 45)	**Proposed Changes**
Expert Discovery		
9a. Opening Expert Reports	December 13, 2024	January 16, 2025
9a. Rebuttal Expert Reports	January 16, 2025	February 14, 2025
9a. Reply Expert Reports	February 14, 2025	March 14, 2025
9a. Expert Deposition Deadline	March 7, 2025	April 4, 2025
9b. Opening *Daubert* Motions	March 28, 2025	April 25, 2025
9b. Answering *Daubert* Briefs	April 17, 2025	May 1, 2025
9b. Reply *Daubert* Briefs	May 1, 2025	May 15, 2025
13. Motions *in Limine* – Meet and confer on motions and briefing schedule	May 2, 2025	May 16, 2025
12. Pretrial Order and Motions *in Limine*	June 9, 2025	No Change
12. Pretrial Conference	June 13, 2025	No Change
15. Trial	June 23, 2025	No Change

Thank you,

Rozzi

From: Preston, Rachel L <RPreston@cooley.com>
Sent: Wednesday, November 13, 2024 11:47 AM
To: Flynn, Michael J. <mflynn@morrisnichols.com>; Adykhuis@mwe.com; McDermott, Sydney <Smcdermott@mwe.com>; kpappas@mwe.com; jvallen@mwe.com; aburrowbridge@mwe.com; Dcarsten@mwe.com; Jackson, William C <WJackson@goodwinlaw.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>
Subject: RE: UTC v. Liquidia (23-975) Nov. 13 M&C

Counsel,

Here is the zoom information for today's M&C:

Topic: 11.13.24 M&C
Time: Nov 13, 2024 02:00 PM Eastern Time (US and Canada)

Join from PC, Mac, Linux, iOS or Android: https://cooley.zoom.us/j/91517704106

Or iPhone one-tap (US Toll): +13126266799,91517704106# or +16469313860,91517704106#

Or Telephone:
Dial:
+1 312 626 6799 (US Toll)
+1 646 931 3860 (US Toll)
+1 301 715 8592 (US Toll)
+1 564 217 2000 (US Toll)
+1 669 444 9171 (US Toll)
+1 253 205 0468 (US Toll)
833 928 4608 (US Toll Free)
833 928 4609 (US Toll Free)
833 548 0276 (US Toll Free)
833 548 0282 (US Toll Free)
Meeting ID: 915 1770 4106
International numbers available: https://cooley.zoom.us/u/aBUGLd8uh

Or an H.323/SIP room system:
H.323: 162.255.37.11 (US West) or 162.255.36.11 (US East)
Meeting ID: 915 1770 4106

SIP: 91517704106@zoomcrc.com

Thanks,
Rachel

From: Flynn, Michael J. <mflynn@morrisnichols.com>
Sent: Wednesday, November 13, 2024 11:35 AM
To: Preston, Rachel L <RPreston@cooley.com>; Adykhuis@mwe.com; McDermott, Sydney <Smcdermott@mwe.com>; kpappas@mwe.com; jvallen@mwe.com; aburrowbridge@mwe.com; Dcarsten@mwe.com; Jackson, William C <WJackson@goodwinlaw.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>
Subject: RE: UTC v. Liquidia (23-975) Nov. 13 M&C

[External]

Rachel,

UTC is available at 2:00 ET for a call on this. Can you please circulate a dial-in?

MICHAEL J. FLYNN
Partner | Morris, Nichols, Arsht & Tunnell LLP
(302) 351-9661 Direct
mflynn@morrisnichols.com

From: Preston, Rachel L <RPreston@cooley.com>
Sent: Wednesday, November 13, 2024 8:57 AM
To: Adykhuis@mwe.com; McDermott, Sydney <Smcdermott@mwe.com>; kpappas@mwe.com; jvallen@mwe.com; aburrowbridge@mwe.com; Dcarsten@mwe.com; Jackson, William C <WJackson@goodwinlaw.com>; Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>
Subject: [EXT] RE: UTC v. Liquidia (23-975) Nov. 13 M&C

Counsel,

Please provide your availability today for the court-ordered meet and confer.

Regards,
Rachel

From: Preston, Rachel L
Sent: Tuesday, November 12, 2024 5:13 PM
To: Adykhuis@mwe.com; McDermott, Sydney <Smcdermott@mwe.com>; kpappas@mwe.com; jvallen@mwe.com; aburrowbridge@mwe.com; Dcarsten@mwe.com; Jackson, William C <WJackson@goodwinlaw.com>; mflynn@morrisnichols.com

Cc: DG-ILD <DG-ILD@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>
Subject: UTC v. Liquidia (23-975) Nov. 13 M&C

Counsel,

We're writing pursuant to the Court's November 8th order (D.I. 190) requiring the parties to engage in a meet and confer re Liquidia's November 8th motion to resolve discovery disputes. Please provide your availability to meet and confer on November 13, as required by the Court. In addition, during the meet and confer we intend to address the extension of fact and expert discovery and the deposition of Dr. Rothblatt. During the call, please confirm your availability to address these issues on November 19, November 21 (2pm or later), November 22, or the date the Court selects.

Regards,
Rachel

Rachel Preston
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Washington, DC 20004-2400
+1 202 776 2315 office
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Pronouns: She, Her, Hers

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EXHIBIT 6

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, V. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 23-975 (RGA) (SRF) [redacted]

EXPERT REPORT OF STEPHAN OGENSTAD, PH.D.

clinical study.[11] Finally, as noted above it is my understanding from counsel that FDA approval is not necessarily a requirement to obtain a patent directed to treating a medical disease, like the claims of the '327 patent.

V. SCIENTIFIC BACKGROUND AND RELATED OPINIONS

A. Pulmonary Hypertension ("PH") Treprostinil

47. I understand from Dr. Channick's report that PH encompasses several conditions that affect the pressure within the blood vessels of the lungs, which can cause patients with PH to experience chest pain, fatigue, fainting spells, shortness of breath, lightheadedness, and swelling in their extremities.[12] These symptoms are attributed to the having a higher than normal pressure in the pulmonary arteries because the additional pressure forces the right side of the heart to work harder to pump blood to the lungs.[13]

48. The World Health Organization ("WHO") classifies the conditions that cause PH into five different "WHO Groups."[14] The classifications depend on the clinical presentation and underlying pathophysiology of the condition, as well as other factors. There were five WHO Groups at the time U.S. Patent No. 11,826,327 ("'327 patent") was filed in April 2020:[15]

- **WHO Group 1: Pulmonary arterial hypertension ("PAH")**. This Group is characterized by abnormal narrowing and thickening of the pulmonary arteries;
- **WHO Group 2: PH due to left heart disease**. This Group includes PH that is caused by dysfunction of the left ventricle of the heart, which leads to increased pressure in the pulmonary arteries;
- **WHO Group 3: PH due to lung diseases and/or hypoxia**. This Group comprises of PH that is due to obstructive lung diseases such as chronic obstructive pulmonary disease ("COPD"), or restrictive lung diseases such as interstitial lung disease ("ILD"). This Group

[11] Channick Opening Report at ¶ 44.
[12] *See* Channick Opening Report at ¶ 12.
[13] *Id.*
[14] *See* Channick Opening Report at ¶ 14.
[15] *See* Channick Opening Report at ¶¶ 14-16.

also comprises of PH that is due developmental lung diseases or hypoxia, which cause low oxygen levels in the blood;

- **WHO Group 4: PH due to pulmonary artery obstructions**. This Group includes chronic thromboembolic PH, which is associated with blood clots in the pulmonary arteries that clog blood flow;

- **WHO Group 5: PH due to unclear and/or multifactorial mechanisms**. This Group includes cases of PH where the underlying cause is either unknown or involves multiple factors like systemic and metabolic disorders, complex congenital heart disease, and hematological disorders.

49. I understand from Dr. Channick's report that Pulmonary Hypertension – Interstitial Lung Disease ("PH-ILD") denotes PH that is caused by ILD, and is classified as part of WHO Group 3.[16] ILD refers to a varied group of progressive lung disorders that are characterized by fibrosis of the lung tissue (i.e., scarring and stiffening) of the lung tissue.[17] The thickening and scarring caused by ILD disorders hinders the flow of oxygen across the alveoli to the blood in vessels of the lung.[18] This reduced oxygen availability often leads to an increase in pressure in the pulmonary circulation, which then leads to that PH. Progressive lung disorders that are associated with ILD include:[19]

- Idiopathic Interstitial Pneumonia ("IIP");
- Chronic Hypersensitivity Pneumonitis;
- Occupational Lung Disease;
- Pulmonary Fibrosis ("PF");
- Idiopathic Pulmonary Fibrosis ("IPF"), which is PF of an unknown cause;
- Combined Pulmonary Fibrosis and Emphysema ("CPFE"); and

[16] *See* Channick Opening Report at ¶¶ 17-22.
[17] *Id.* at ¶ 18.
[18] *Id.*
[19] *Id.*; *see also* '327 patent at 2:53-3:2 12:49-62; 18:6-14.

- Connective Tissue Disease ("CTD")

50. I understand from Dr. Channick's report that PH that is associated with the progressive lung disorders above is considered PH-ILD.[20] Accordingly, PH caused by CPFE ("PH-CPFE") would be considered PH-ILD.[21]

B. Treprostinil

51. Treprostinil is the active ingredient in several approved therapies for pulmonary arterial hypertension.[22] In 2002 and 2004, the FDA approved the subcutaneous and intravenous administration of treprostinil to "diminish symptoms associated with exercise" in patients with pulmonary arterial hypertension ("PAH").[23] In 2009, the FDA approved Tyvaso®, an inhaled version of treprostinil, for treating "pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance."[24] As a liquid formulation of treprostinil, Tyvaso® was administered through a pulsed nebulizer as a mist.[25] In 2021, Tyvaso® received FDA approval to "improve exercise ability" in patients with PH-ILD.[26] And in 2022, a different formulation of Tyvaso® was approved for administration as a dry-powder inhalant under the brand name Tyvaso DPI®.[27]

52. The FDA approval history of treprostinil shows that by 2020, both injectable and inhaled forms of treprostinil were already approved for use in patients with PH.[28] Specifically, the

[20] Channick Opening Report at ¶ 18.
[21] Channick Opening Report at ¶ 18.
[22] '327 patent at 8:1-18.
[23] I understand that the FDA approved treprostinil under the brand name Remodulin® for subcutaneous and intravenous administration. *See* 2009 Tyvaso® Label (UTC_PH-ILD_010692) at UTC_PH-ILD_010693; Remodulin Label, NDA 21-272/S-005 (LIQ_PH-ILD_00002444) at 6; '327 patent at 8:1-18.
[24] 2009 Tyvaso® Label (UTC_PH-ILD_010692) at UTC_PH-ILD_010693.
[25] *Id.* at UTC_PH-ILD_010693–94.
[26] 2021 Tyvaso® Label (UTC_PH-ILD_010744) at UTC_PH-ILD_010744.
[27] 2023 Tyvaso® Label (UTC_PH-ILD_010726) at UTC_PH-ILD_010727.
[28] Channick Opening Report at ¶¶ 24-25.

first injectable form of treprostinil (Remodulin®) was approved as early as 2002 and 2004, while the first inhaled form of treprostinil (Tyvaso®) was approved as early as 2009.[29]

53. As I discuss in more detail below in the context of the relevant prior art, by 2020 the use of treprostinil specifically in PH Group 3 and/or PH-ILD patients was widespread and had been the subject of several public research reports, conference presentations, and public commentary by UTC and others. (*See* Section V.D below.)

54. I further note that leading clinicians in the relevant field had, before 2020, made public statements regarding the use of treprostinil in PH-ILD patients that would have informed a POSA. Indeed, as I explain below, the history of development of inhaled treprostinil as a treatment to improve exercise capacity in PH-ILD patients was based on the very same clinical evidence that Dr. Thisted now discounts as unreliable and flawed. (*See* Sections V.D, V.E, and V.F below.)

C. The Drug Development Process

55. In this section I provide a general description of the process for development of therapies for use in humans. As noted in the Legal Standards discussion above, the level of scientific rigor and sufficiency of evidence typically required for FDA approval of a drug is distinct from the level of evidence relevant for the patentability of an invention.

1. Phase I-III Clinical Trials

56. Phase I trials are concerned primarily with establishing a new drug's safety and dose range in about 20-100 healthy volunteers (or patients, in the context for example of oncology trials).

57. Phase II studies determine the effectiveness of an experimental drug on a particular disease or condition in approximately 100 to 300 volunteers. Phase II clinical trials are designed

[29] Channick Opening Report at ¶¶ 24-25; *see* 2009 Tyvaso® Label (UTC_PH-ILD_010692); Remodulin Label, NDA 21-272/S-005 (LIQ_PH-ILD_00002444) at 6; '327 patent at 8:1-18.

observed survival to expected benchmarks, or a Cox Proportional Hazards Model, which evaluates the association between treatment and time-to-event outcomes while adjusting for covariates. Under appropriate circumstances, a statistician may also employ Bayesian approaches such as Bayesian posterior probability, which provides probability estimates for treatment efficacy, incorporating prior knowledge or historical data.

D. Disclosures of the Relevant Prior Art References Related to Treprostinil Studies and PH-ILD

95. In this section I outline a summary of the disclosures of the relevant prior art references. In formulating these summaries, I relied on my own review of the references, in addition to Dr. Channick's discussion of them in his opening expert report.[48]

96. Dr. Thisted offers several critiques Dr. Channick's opinions relating to these prior art references, which I respond to in Section VI, below.

1. '793 Patent

97. U.S. Patent No. 10,716,793 (the "'793 patent"), entitled "Treprostinil Administration by Inhalation," was filed on January 31, 2020 and granted on July 21, 2020.[49] The '793 patent "claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006" and "U.S application Ser. No. 11/748,205, filed May 14, 2007," and several other applications dated between 2009 to 2019.[50] Counsel has informed me that the '793 patent is assigned to UTC, and qualifies prior art based on at least its May 14, 2007 priority date. [redacted]

[redacted]

[48] *See, e.g.,* Channick Opening Report at ¶¶ 119-127 (Faria-Urbina 2018), ¶¶ 217-221 (Agarwal 2015), ¶¶ 222-240 ('793 Patent), ¶¶ 256-259 (Parikh 2016), and ¶¶ 308-316 (Saggar 2014).
[49] '793 patent at Cover.
[50] *Id.* at 1:7-16.

[redacted].[51]

98. The '793 patent has 8 claims, which I have reproduced below for context:

> 1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.
>
> 2. The method of claim 1, wherein the inhalation device is a soft mist inhaler.
>
> 3. The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.
>
> 4. The method of claim 1, wherein the inhalation device is a dry powder inhaler.
>
> 5. The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.
>
> 6. The method of claim 4, wherein the formulation is a powder.
>
> 7. The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.
>
> 8. The method of claim 1, wherein the formulation contains no metacresol.

I understand from Dr. Channick that the claims of the '793 patent encompass a method of using inhaled treprostinil to treat PH-ILD patients and improve their exercise capacity.[52] I understand that Dr. Waxman has taken this same position in a report he prepared for UTC regarding the '793 patent in an IPR proceeding.[53] And I understand that UTC submitted a letter to the FDA indicating that the claims of the '793 patent cover the PH-ILD indication for Tyvaso, an indication which

[51] Maebius Depo. Tr. at 87:2-13.
[52] Channick Opening Report at ¶ 229.
[53] Hill Opening Report at ¶¶ 262-263; *see also* Waxman IPR Decl. (LIQ_PH-ILD_00102032) at ¶ 95-96.

reads: "[p]ulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability."[54]

99. Claim 1 of the '793 patent recites the "administering by inhalation" of "15 micrograms to 90 micrograms" of treprostinil "in 1 to 3 breaths." I agree with Dr. Channick that inhaling 15 mcg across 1 to 3 breaths meets the "at least 6 micrograms per breath" limitation of claim 1 of the '327 patent.[55] I further understand from Dr. Channick that a POSA "would have understood that pulmonary fibrosis as described in the '793 patent is a form of PH-ILD, and that PH-ILD patients were treated in the '793 patent examples."[56]

2. Saggar 2014

100. Saggar 2014 is an article titled "Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis." The article was published in 2014 in volume 69 of Thorax on pages 123–129.

101. Saggar 2014 is a study where parenteral treprostinil was administered in 15 patients with pulmonary fibrosis and advanced PH.[57] Table 1 from Saggar 2014 lists patient demographics, including the underlying fibrotic lung disease clinical subtypes.

[54] Channick Opening Report at ¶ 228; *see also* Feb. 12 2024, [redacted] (LIQ_PH-ILD_00000847) at LIQ_PH-ILD_00000852.
[55] Channick Opening Report at ¶ 232.
[56] Channick Opening Report at ¶ 237.
[57] Saggar 2014 at LIQ_PH-ILD_00000227.

Table 1 Patient demographics, underlying fibrotic lung disease clinical subtype, and background PH-targeted therapy

	N=15	
Patient characteristics	**Mean**	**SD**
Age in years	63	15
	N	**Per cent**
NYHA class		
III	8	53
IV	7	47
Race		
Hispanic	8	53
Caucasian	4	27
Filipino/Japanese	2	13
Middle Eastern	1	7
Fibrotic lung disease clinical subtype		
Idiopathic pulmonary fibrosis	8	53
NSIP-fibrosis	2	13
PF/emphysema (CPFE)	3	20
Chronic Hypersensitivity Pneumonitis (HP)	1	7
Silicosis	1	7
Background therapy		
Sildenafil monotherapy	4	27
Bosentan monotherapy	2	13
Sildenafil/bosentan combination	3	20
None	6	40

CPFE, combined pulmonary fibrosis/emphysema; NSIP, non-specific interstitial pneumonia; NYHA, New York Heart Association; PF, pulmonary fibrosis; PH, pulmonary hypertension.

I understand from Dr. Channick that the fibrotic lung disease of the 15 patients are various types of ILD.[58] I further understand from Dr. Channick that because the 15 patients all had ILD and PH, the Saggar 2014 studied administering parenteral treprostinil in 15 patients with PH-ILD.[59]

102. Saggar 2014 reports patient 6MWD, Forced Vital Capacity ("FVC"), haemodynamics, and plasma concentration of NT-proBNP results following 12 weeks of administering parenteral treprostinil. With respect to 6MWD, Saggar 2014 reports "6MWD improvements following 12 weeks of parenteral treprostinil therapy (mean 59 m; $p<0.001$)."[60] These 6MWD results are also shown in Table 2 in Saggar 2014:[61]

[58] Channick Opening Report at ¶¶ 308-316; Saggar 2014 at LIQ_PH-ILD_00000227.
[59] Channick Opening Report at ¶¶ 308-316; Saggar 2014 at LIQ_PH-ILD_00000227.
[60] *Id.* at LIQ_PH-ILD_00000229.
[61] *Id.* at LIQ_PH-ILD_00000228 (Table 2).

Table 2 Pulmonary function testing, oxygen requirements, and 6 min walk distance with Borg Dyspnoea Index (BDI) scores at baseline and end of study

	Baseline N=15 Mean (SD)	12 weeks N=15 Mean (SD)	p Value*
Pulmonary function			
FVC, % predicted	62 (21)	63 (18)	0.687
FEV_1, % predicted	62 (17)	64 (16)	0.215
FEV_1/FVC	77 (11)	80 (12)	0.134
TLC, % predicted			
All patients	70 (15)	–	
Patients without CPFE, n=12	67 (16)	–	
DLCO, % predicted†	24 (13)	22 (11)	0.206†
FVC%/DLCO%†	2.5 (2.4)	3.0 (1.6)	0.625†
Oxygen flow (L/min)	3.9 (1.9)	3.9 (2.1)	>0.999
6 min walk:			
6 min walk distance (m)	171 (93)	230 (114)	<0.001
Room air % saturation	83 (7)	80 (10)	0.078
10 L face mask, % saturation†	98 (3)	99 (4)	0.372†
10 L face mask, % saturation nadir	85 (9)	82 (10)	0.084
BDI score	13.7 (2.3)	13.1 (2.6)	0.203

*Paired t test p value presented, except when Wilcoxon signed rank indicated.
†Data are non-normally distributed; median (IQR) and Wilcoxon signed rank p value presented.
CPFE, combined pulmonary fibrosis emphysema; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.

103. With respect to FVC, Table 2 from Saggar 2014 also shows an average change in predicted FVC percent from 62% at baseline to 63% after 12 weeks of administering parenteral treprostinil.[62] Table 3 from the Appendix of Saggar 2014 provides more detail regarding the predicted FVC results for each patient:[63]

	Week	Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pulmonary Function																
FVC, % Predicted	0	57	38	78	54	69	57	50	88	58	77	37	105	84	44	38
	12	66	33	82	62	74	64	54	66	63	82	38	94	84	44	41

The 1% change in FVC predicted percent is comparable to the 1.1% change described in the

[62] *Id.*
[63] *Id.* at LIQ_PH-ILD_00000243 (Table 3: Pulmonary function testing, oxygen requirements, and 6 minute walk distance with Borg dyspnea index scores at baseline and end of study)

INCREASE Study, which I explain in more detail below.[64]

104. With respect to hemodynamics, Saggar 2014 reports that patients showed "significant improvements were demonstrated in right heart haemodynamics" after 12 weeks of administering parenteral treprostinil.[65] These results are listed in Table 4 of Saggar 2014:[66]

Table 4 Systemic and pulmonary haemodynamics and oxygenation at baseline compared with 12 weeks after parenteral treprostinil therapy

	Baseline N=15 Mean (SD)	12 weeks N=15 Mean (SD)	p Value*
Haemodynamics, mm Hg			
Right atrial pressure	9.5 (3.4)	6.0 (3.7)	<0.001
Mean pulmonary pressure	47.0 (8.0)	38.9 (13.4)	0.005
Pulmonary artery wedge pressure	12.5 (4.1)	10.5 (6.1)	0.247
Cardiac output (L/min)	4.3 (1.1)	4.9 (1.1)	0.042
Cardiac index (L/min/m^2)	2.3 (0.5)	2.7 (0.6)	0.017
PVR (dyn s/cm^5)	698 (278)	496 (229)	<0.001
Mixed venous O_2 saturation (%)	65 (7.2)	70.9 (7.4)	0.023
Haemoglobin (g/dL)	14.1 (2.1)	13.6 (2.2)	0.310
Arterial O_2 content (mL O_2/100 mL)	16.6 (3.1)	15.4 (3.6)	0.086
O_2 delivery (mL/min)†	6332 (2295)	7263 (5337)	0.246†
Pulmonary capacitance (mL/mm Hg)‡	1.28 (0.54)	1.64 (0.91)	0.013
RV pulsatility	0.94 (0.16)	1.04 (0.16)	0.010
Pulse pressure	44.1 (8.9)	40.3 (14.1)	0.182
Stroke volume (mL) †	51.8 (8.7)	61.8 (21.7)	0.031†
Stroke volume index	29.2 (6.7)	33 (7.3)	0.037
Systolic blood pressure†	125 (25)	109 (13)	0.028†
Mean arterial pressure	88.6 (15.8)	84.8 (9.4)	0.278
HR (beats/min)	79 (9.9)	80 (11.8)	0.490
Rs (dyn s/cm^5)	1575 (487)	1306 (357)	0.015
PVR/SVR	0.46 (0.13)	0.39 (0.15)	0.060
TPG	34.7 (8.7)	28.5 (10.3)	0.014
BNP (pg/mL)	558 (859)	228 (340)	0.004†

*Paired t test p value presented, except when Wilcoxon signed rank indicated.
†Data are non-normally distributed; median (IQR) and Wilcoxon signed rank p value presented.
‡Pulmonary capacitance = stroke volume/pulse pressure.
BNP, brain natriuretic peptide; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance; TPG, transpulmonary gradient.

105. With respect to plasma concentration of NT-proBNP, I understand from Dr. Channick's report that BNP and NT-proBNP are regarded as interchangeable in the clinical

[64] NEJM Publication at UTC_PH-ILD_010825 (Table S6).
[65] Saggar 2014 (LIQ_PH-ILD_00000226) at LIQ_PH-ILD_00000230.
[66] *Id.*

context.[67] As shown above, Table 4 from Saggar 2014 reports measurements of BNP ("brain natriuretic peptide") in the 15 patients fell from 558 pg/ml to 228 pg/ml.[68]

106. [redacted]

3. Parikh 2016

107. Parikh 2016 is an article titled "Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension." The article was published in 2016 in Volume 67 Issue 4 of the *Journal of Cardiovascular Pharmacology* on pages 322-325.[71] I note my understanding that Dr. Victor Tapson, an INCREASE steering committee member, is a co-author of Parikh 2016

108. Parikh 2016 discloses a retroactive study of treating 80 PH patients with inhaled treprostinil.[72] Out of the patients studied, at least 6 out of the 25 patients with WHO Group 3 PH were considered to have PH-ILD:[73]

[67] Channick Opening Report at ¶ 312.
[68] Saggar 2014 at LIQ_PH-ILD_00000230 (Table 4).
[69] Channick Opening Report at ¶ 264; Investigator Brochure UTC_PH-ILD_082805 at UTC_PH-ILD_082814.
[70] Channick Opening Report at ¶ 264; Investigator's brochure at UTC_PH-ILD_082813.
[71] K. Parikh., et al., Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension, *J. Cardiovasc. Pharmacol.* 67(4); 322–25 (2016) ("Parikh 2016") (UTC_PH-ILD_010599).
[72] *Id.* at UTC_PH-ILD_010599.
[73] *Id.* at UTC_PH-ILD_010607.

PH World Health Organization Classification	
• Group 1	41 (51.9)
◦ Idiopathic	16 (40.0)
◦ Familial	1 (2.5)
◦ Drug/toxin-induced	2 (5.0)
◦ Connective tissue disease	15 (37.5)
◦ Human Immunodeficiency Virus	2 (5.0)
◦ Portopulmonary hypertension	1 (2.5)
◦ Congenital heart disease	3 (7.5)
• Group 2	3 (3.8)
• Group 3	25 (31.6)
◦ Obstructive disease	13 (52.0)
◦ Interstitial lung disease/fibrosis	6 (24.0)
◦ Mixed pattern	6 (24.0)
• Group 4	9 (11.4)
• Group 5	1 (1.3)

The treatment studied in Parikh 2016 involved an initial dosing regimen of a single administration of 3 breaths (18 mcg) per session, which was then increased to 6 breaths (36 mcg) in the second session.[74] Following the initial dosing regimen, the doses were titrated up by 1 breath every day until patients received a dose of 12 breaths (72 mcg) four times per day.[75] This dosing protocol was described in Figure 1 from Parikh 2016:[76]

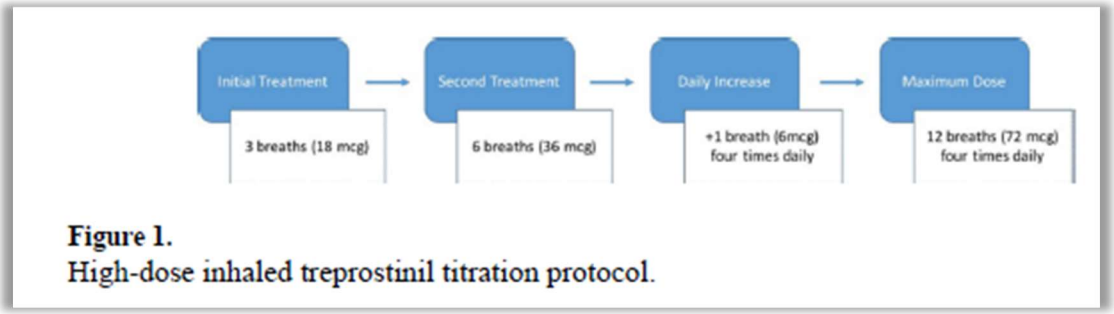


Figure 1.
High-dose inhaled treprostinil titration protocol.

109. While the primary endpoints of the study were safety and tolerability, data related PH severity was also reported—including 6MWD, Dyspnea-Fatigue Index Score, and amino-

[74] *Id*. at UTC_PH-ILD_010600 (Methods, Study Population).
[75] *Id*. at UTC_PH-ILD_010600 (Methods, Study Population).
[76] *Id*. at UTC_PH-ILD_010606 (Figure 1).

terminal pro-B-type natriuretic peptide (NT-proBNP) value.[77] Parikh 2016 discloses this data under the "Efficacy Parameters" section:[78]

Efficacy Parameters

Routinely used measures including 6-minute walk distance, Borg dyspnea index, and NT-proBNP were tracked over time as biomarkers of PH severity. The average change in 6-minute walk distance was 3.9 meters (95% confidence interval: −13.4, 21.2) from Baseline to Follow-up 1 (n=39; p=0.65), and 31.6 meters (−3.8, 67.0) from the Baseline to Follow-up 2 (n=34; p=0.08). Mean Borg Dyspnea Index changed by −0.2 (−0.7, 0.2) (n=37; p=0.31) and 0.0 (−0.76, 0.76) (n=32; p=1.00) between corresponding visits. Finally, NT-proBNP decreased by 39 ng/L (−312, 234) at Follow-up 1 (n=32, p=0.77) and 630 ng/L (−1456, 197) at Follow-up 2 (n=23, p=0.13).

Parikh 2016 reported that patient 6MWD increased by an average of 3.9 meters from baseline at follow-up visit 1 (n = 39; p = 0.65), and 31.6 meters from baseline at follow-up visit 2 (n = 34; p = 0.08).[79] Parikh 2016 further reports that NT-proBNP decreased by 39 ng/L at Follow-up Visit 1 and 630 ng/L at Follow-up 2.[80] Based on this data, I understand that the authors concluded that inhaled treprostinil had "favorable safety and tolerability profile among PH WHO group 3 patients in [the] study for whom there are currently no approved therapies, and [inhaled treprostinil] may provide benefit in this patient population."[81]

4. Agarwal 2015

110. Agarwal 2015 is an abstract of an article titled "Inhaled Treprostinil in Group-3

[77] *Id*. at UTC_PH-ILD_010601 (Endpoints).
[78] *Id*. at UTC_PH-ILD_010602 (Efficacy Parameters).
[79] Channick Opening Report at ¶ 258; *see also* Parikh 2016 at UTC_PH-ILD_010601 (Results), UTC_PH-ILD_010602 (Efficacy Parameters).
[80] Channick Opening Report at ¶ 258; *see also* Parikh 2016 at UTC_PH-ILD_010602 (Efficacy Parameters).
[81] Channick Opening Report at ¶ 258; *see also* Parikh 2016 at UTC_PH-ILD_010603.

Pulmonary Hypertension."[82] The abstract was published in April 2015.[83] Dr. Waxman is a co-author on Agarwal 2015.[84]

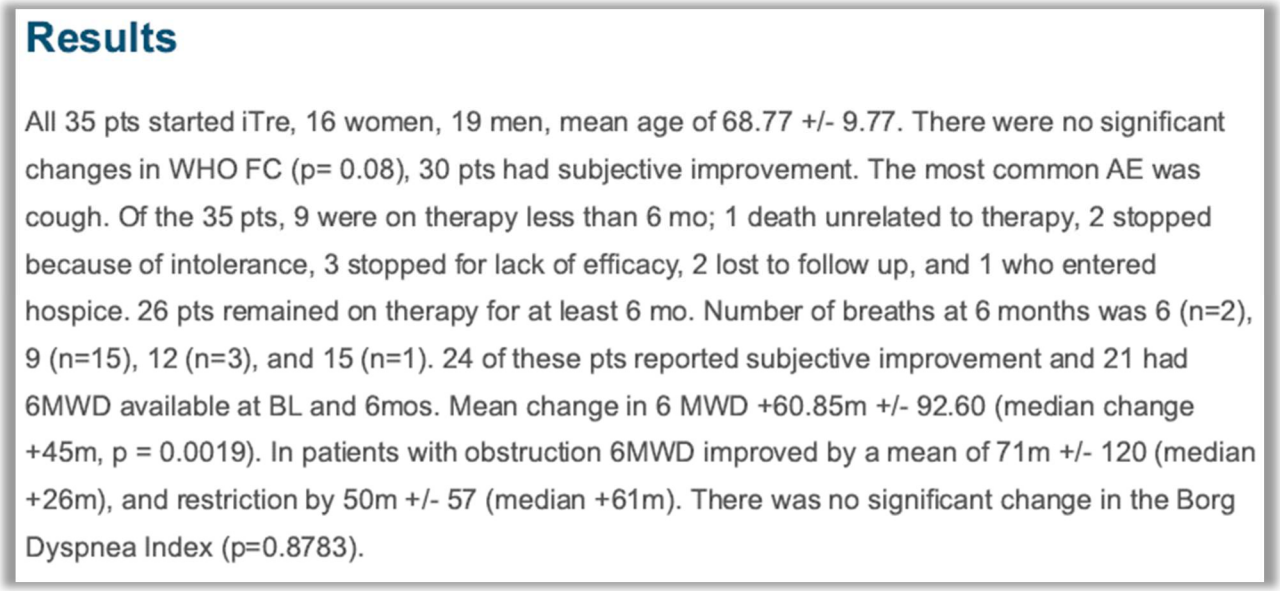
111. Agarwal 2015 discloses a retrospective study of Group 3 PH patients receiving inhaled treprostinil.[85] A total of 35 PH patients were treated as part of the study: 15 were classified as obstructive Group 3 PH patients, 15 were classified as restrictive Group 3 PH patients, and 5 were classified as mixed obstructive/restrictive.[86]

112. Patients in the study started on 3 breaths of inhaled treprostinil 4 times a day, and moved up to a total of 9-12 breaths of inhaled treprostinil 4 times a day.[87] I understand that Dr. Waxman, one of the authors who administered the study in Agarwal 2015, has testified that the study used the standard dosing from the 2009 Tyvaso® label.[88] I understand from Dr. Channick's report that this means each breath the patients took delivered 6 mcg of inhaled treprostinil.[89] Accordingly, at 9 breaths per treatment session, a patient would receive a total of 216 mcg of inhaled treprostinil per day across four treatment sessions.[90] If a patient took 12 breaths per treatment session, the patient would receive a total of 288 mcg of inhaled treprostinil per day across four treatment sessions.[91]

113. The "Results" section of Agarwal 2015 reports the patients' 6 MWD and other

[82] *See* Agarwal 2015 (LIQ_PH-ILD_00001400); LIQ_PH-ILD_00148508 (abstract); UTC_PH-ILD_009828 (abstract).
[83] *Id.*
[84] *Id.*
[85] *Id.*
[86] Agarwal 2015 (LIQ_PH-ILD_00001400) at LIQ_PH-ILD_00001401.
[87] *Id.*
[88] Waxman Depo. Tr. at 57:10-23.
[89] 2009 Tyvaso® label at UTC_PH-ILD_010693 ("Dosing and Administration"); *see* Waxman Depo. Tr. at 57:10-59:12.
[90] Channick Opening Report at ¶ 220.
[91] *Id.*

measures following the administration of inhaled treprostinil:



Results

All 35 pts started iTre, 16 women, 19 men, mean age of 68.77 +/- 9.77. There were no significant changes in WHO FC (p= 0.08), 30 pts had subjective improvement. The most common AE was cough. Of the 35 pts, 9 were on therapy less than 6 mo; 1 death unrelated to therapy, 2 stopped because of intolerance, 3 stopped for lack of efficacy, 2 lost to follow up, and 1 who entered hospice. 26 pts remained on therapy for at least 6 mo. Number of breaths at 6 months was 6 (n=2), 9 (n=15), 12 (n=3), and 15 (n=1). 24 of these pts reported subjective improvement and 21 had 6MWD available at BL and 6mos. Mean change in 6 MWD +60.85m +/- 92.60 (median change +45m, p = 0.0019). In patients with obstruction 6MWD improved by a mean of 71m +/- 120 (median +26m), and restriction by 50m +/- 57 (median +61m). There was no significant change in the Borg Dyspnea Index (p=0.8783).

114. I understand from Dr. Channick that data in Agarwal 2015 was later cited as one of the studies that formed UTC's rationale for pursuing the INCREASE Study.[92] [redacted].[94]

5. Faria-Urbina 2018

115. Faria-Urbina 2018 is an article titled "Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease." The article was published in 2018 in volume 196

[92] Channick Opening Report at ¶ 261; Waxman Depo. Tr. at 169:1-11; NEJM Publication at UTC_PH-ILD_010791.
[93] Channick Opening Report at ¶ 264; Investigator Brochure UTC_PH-ILD_082805 at UTC_PH-ILD_082814; *see also* Tapson Depo. Tr. at 80:1-80:19 ([redacted]), 80:22 – 81:23 ([redacted]).
[94] Channick Opening Report at ¶ 264; Investigator's brochure at UTC_PH-ILD_082813-814.

of the *Lung* journal on pages 139-146.[95] Dr. Waxman is identified as senior author of Faria-Urbina 2018.[96]

116. Faria-Urbina 2018 discloses a retrospective study of 72 PH patients treated with inhaled treprostinil.[97] I understand for Dr. Channick that 9 of these patients were classified as having PH-ILD.[98] I further understand that 5 patients were classified as having PH-CPFE.[99] The diagram from Faria-Urbina, reproduced below, provides more detail about the patients in the study:

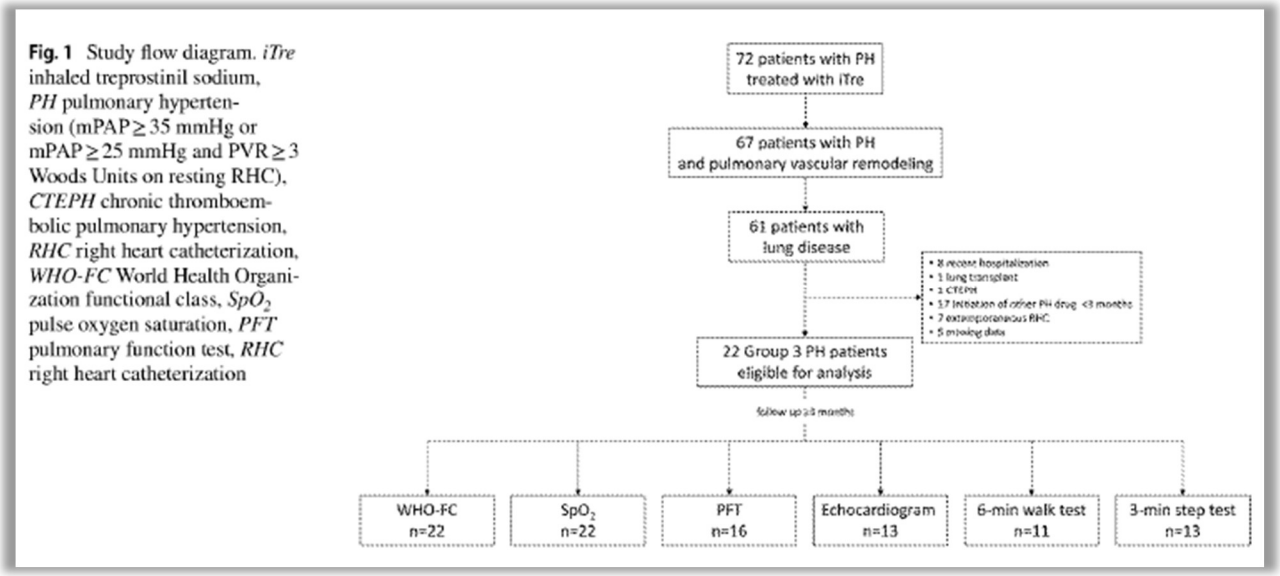


Fig. 1 Study flow diagram. *iTre* inhaled treprostinil sodium, *PH* pulmonary hypertension (mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg and PVR ≥ 3 Woods Units on resting RHC), *CTEPH* chronic thromboembolic pulmonary hypertension, *RHC* right heart catheterization, *WHO-FC* World Health Organization functional class, SpO_2 pulse oxygen saturation, *PFT* pulmonary function test, *RHC* right heart catheterization

117. Patient measures included WHO-FC, 6MWD, and FVC (% predicted). These results are listed in Table 2 which I have reproduced below:[100]

[95] M. Faria-Urbina, et al., Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease, Lung 196:139–146 (2018) ("Faria-Urbina 2018") (UTC_PH-ILD_009936).
[96] Faria-Urbina 2018 at UTC_PH-ILD_009936.
[97] Faria-Urbina 2018 at UTC_PH-ILD_009936.
[98] Channick Opening Report at ¶ 121.
[99] Faria-Urbina 2018 Supplemental Materials at UTC PH-ILD 219378.
[100] Faria-Urbina 2018 (UTC_PH-ILD_009936) at UTC_PH-ILD_009940 (Table 2).

Table 2 Changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil

	N	Baseline	Follow-up	*p* value
Clinical assessment	22			
WHO functional class I/II/III/IV (n)		0/4/15/3	2/7/12/1	0.041
SpO_2 at rest (%)		92 ± 6	94 ± 4	0.014
Pulmonary function test	16			
FEV_1 (% predicted)		65 ± 27	60 ± 25	0.23
FVC (% predicted)		67 ± 26	59 ± 22	0.12
FEV_1/FVC (% predicted)		96 ± 15	96 ± 18	0.99
Echocardiography	13			
TRV (m/s)		3.7 ± 0.5	3.6 ± 0.5	0.66
Estimated sPAP (mmHg)		62 ± 18	60 ± 22	0.68
6-min walk test	11			
Distance (m)		243 ± 106	308 ± 109	0.022
Final dyspnea Borg score		6 ± 2	4 ± 2	0.15
Final SpO_2 (%)		82 ± 8	76 ± 9	0.12
3-min step test with metabolic cart	13			
VE/VCO_2 slope		45.9 ± 19.7	47.8 ± 20.1	0.55
Δ $P_{ET}CO_2$ (mmHg)		0.0 ± 1.9	-0.9 ± 2.6	0.081
Final SpO_2 (%)		81 ± 8	80 ± 7	0.76

Data are presented as *n* or mean ± SD

WHO World Health Organization, *SpO_2* arterial oxygen saturation measured by pulse oximetry, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *TRV* tricuspid regurgitant jet velocity, *sPAP* systolic pulmonary arterial pressure, *VE* minute ventilation, *VCO_2* carbon dioxide production, Δ change in, *$P_{ET}CO_2$* end-tidal carbon dioxide tension

As seen in Table 2 from Faria-Urbina 2018, patients receiving inhaled Treprostinil showed a statistically significant improvement in 6MWD (n = 11; *p*-value = 0.022) and WHO-FC (n = 22; *p*-value = 0.041).[101]

6. February 2020 Press Release

118. On February 24, 2020 UTC issued a press release titled "United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints" (the "Feb. 2020 Press Release").[102] The Feb. 2020 Press Release discloses the results of the INCREASE Study, which found that "Tyvaso increased six-minute walk distance by 21 meters

[101] Faria-Urbina 2018 at UTC_PH-ILD_009940 (Table 2).
[102] United Therapeutics, *United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints*, https://ir.unither.com/press-releases/2020/02-24-2020-161749814 (Feb. 24, 2020) ("Feb. 2020 Press Release") (UTC_LIQ00063612).

versus placebo (p=0.0043, Hodges-Lehmann estimate) after 16 weeks of treatment."[103] It further discloses that "[s]ignificant improvements were also observed in each of the study's secondary endpoints including reduction in the cardiac biomarker NT-proBNP, time to first clinical worsening event, change in peak 6MWD at Week 12, and change in trough 6MWD at week 15."[104] Dr. Smith, an inventor on the '327 patent, testified that the "significant improvement" language was meant to convey the results were statistically significant.[105]

E. Additional Evidence as of 2020 Supporting the Use of Inhaled Treprostinil in PH-ILD Patients

119. I understand from Dr. Channick that in addition to the studies discussed above, other pre-2020 studies and evidence show that POSAs expected inhaled treprostinil would successfully treat PH-ILD before 2020 because treprostinil had already demonstrated success in treating other forms of PH within WHO Group 3, which includes PH-ILD.[106] In the following sections, I summarize the studies, documents, and deposition testimony that Dr. Channick has identified as evidence that POSAs expected inhaled treprostinil to treat PH-ILD before 2020 because treprostinil had already demonstrated success in treating other forms of PH that fell within WHO Group 3.

1. Pre-2020 Studies Reported Positive Results from Using Treprostinil to Treat WHO Group 3 Patients, Including Those With PH-ILD.

a. Parenteral Treprostinil Demonstrated Successful Treatment of WHO Group 3 Patients in Pre-2020 Studies

120. In addition to Saggar 2014, many other pre-2020 studies reported positive results from using parenteral treprostinil to treat WHO Group 3 patients.[107] One of the authors of Saggar

[103] Feb. 2020 Press Release at UTC_LIQ00063612.
[104] Feb. 2020 Press Release at UTC_LIQ00063612.
[105] Smith Depo Tr. at 215:21-216:10.
[106] Channick Opening Report at ¶ 28.
[107] Channick Opening Report at ¶¶ 28-31.

2014, Dr. Rajan Saggar, had also authored an 2009 article titled "Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation" ("Saggar 2009").[108] The Saggar 2009 study, which was funded by UTC research grant, reported that parenteral treprostinil improved a patient's 6MWD, WHO functional class, BNP level, quality of life survey score, Borg Dyspnea Scale, and spirometric function, including an improvement in FVC.[109]

121. As another example, a 2013 patent application by UTC claimed, "[a] method of treating a condition associated with an interstitial lung disease, comprising parenteral administration to subject in need thereof an effective amount of [t]reprostinil. . . wherein said condition is pulmonary hypertension, which [is] a complication of said interstitial lung disease."[110] I understand from Dr. Channick that the patent application disclosed studies showing a positive effect of intravenous treprostinil in patients with IPF and PH.[111] I further understand from Dr. Channick's report that Dr. Michael Wade, a named inventor of the 2013 patent application, testified that his patent application discloses the use of treprostinil for the treatment of ILD and the use of inhaled treprostinil for this disease.[112]

122. And as explained in more detail below, the Saggar 2014 study, which was partly funded by UTC, reported "significant improvements in right heart h[e]modynamics," "improvements [] in 6MWD," quality of life indices as measured in the 36-Item Short Form Health

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[108] R. Saggar, et al., Treprostinil to Reverse Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis as a Bridge to Single-Lung Transplantation, *J. Heart and Lung Transplant.* 28:964-7 (2009) (LIQ_PH-ILD_00002986) ("Saggar 2009") at 965; Channick Opening Report at ¶ 29.
[109] *Id*.
[110] Channick Opening Report at ¶ 31; U.S. Patent Application Ser. No. US 2013/0096200 A1 ("Wade 200") (UTC_PH-ILD_010774) at Claim 1.
[111] Channick Opening Report at ¶ 31; Wade 200 at [0082].
[112] Channick Opening Report at ¶ 31; Wade Depo. Tr. at 35:15-25; 36:19-22; 38:12-1.

Survey Mental Component Summary aggregate and University of California, San Diego Shortness of Breath Questionnaires, as well as in BNP levels.[113] Saggar 2014 further reported an improvement in percent predicted FVC following treprostinil treatment.[114]

b. Inhaled Treprostinil Demonstrated Successfully Treatment of WHO Group 3 Patients In Pre-2020 Studies

123. In addition to the Parikh 2016, Agarwal 2015, and Faria-Urbina 2018 studies discussed above, many other pre-2020 studies reported positive results from using inhaled treprostinil to treat WHO Group 3 PH patients.[115]

124. For example, Drs. Schirro and Waxman authored a 2011 article titled "Inhaled treprostinil therapy in patients with pulmonary hypertension and parenchymal lung disease" (the "Schirro and Waxman 2011" article), which reported that administering inhaled treprostinil according to the "usual protocol starting with three breaths four times a day," in PH patients with parenchymal lung disease (a form of Group 3 PH) improved patient 6MWD and Borg Dyspnea Scale scores.[116] Based on these findings, the authors of the 2011 study concluded that inhaled treprostinil "may offer an effective and well tolerated treatment in subjects with PLD and shortness of breath exacerbated by PH."[117]

[113] Saggar 2014 at LIQ_PH-ILD_00000226, LIQ_PH-ILD_00000228 (Tbl. 2), LIQ_PH-ILD_00000229, LIQ_PH-ILD_00000231; Channick Opening Report at ¶ 30.
[114] Saggar 2014 at LIQ_PH-ILD_00000228 (Tbl. 2); Channick Opening Report at ¶ 30.
[115] Channick Opening Report at ¶¶ 32-35.
[116] Channick Opening Report at ¶ 32; A. Schirro and A. Waxman, Inhaled treprostinil therapy in patients with pulmonary hypertension and parenchymal lung disease, *Eur. Respir. J.* 38:p2385 (2011) (LIQ_PH-ILD_00002474) ("Schirro and Waxman 2011") at Abstract; *see also Eur. Respir. J.* Vol. 38 Suppl. 55 Table of Contents (LIQ_PH-ILD_00002462).
[117] Schirro and Waxman 2011 at Abstract; *see also Eur. Respir. J.* Vol. 38 Suppl. 55 Table of Contents (LIQ_PH-ILD_00002462).

c. The Demonstrated Success of Treprostinil in Single-Arm Pre-2020 Studies Spurred Physicians to Use Treprostinil Off-Label to Treat PH-ILD Patients

125. I understand from Dr. Channick that due to the positive results of pre-2020 studies of using treprostinil to treat WHO Group 1 PH patients, clinics began to use treprostinil for treating patients outside of Group 1 PH, including Group 3 PH patients with PH-ILD.[118] For example, a 2015 survey of 30 U.S. pulmonary vascular disease centers showed that they used PAH therapy, including treprostinil, to treat patients with non-group 1 PH.[119] Additionally, the 2017 Giessen PH registry showed that 78% of WHO Group 3 patients, including PH-ILD patients, were on PAH therapies.[120]

126. I also understand from Dr. Channick that he and other physicians "regularly prescribed inhaled treprostinil to PH-ILD patients off-label" and "before the April 2020 priority date of the '327 patent, before the results of the INCREASE trial were published, and before Tyvaso® was approved for the treatment of PH-ILD" because of the positive results of pre-2020 studies of using treprostinil to treat WHO Group 1 PH patients.[121]

127. For example, Drs. Rajeev Saggar and Rajan Saggar, who were among the authors of Saggar 2014, testified that they used treprostinil off-label to treat non-Group 1 PH patients, including PH-ILD patients.[122] Dr. Rajeev Saggar testified that he had used Tyvaso off-label to

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[118] Channick Opening Report at ¶ 36.

[119] A. W. Trammell, et al., Use of pulmonary arterial hypertension-approved therapy in the treatment of non-group 1 pulmonary hypertension at US referral centers, *Pulm. Circ.* 5(2):356-63 (2015) (LIQ_PH-ILD_00002539) ("Trammel 2015"); Channick Opening Report at ¶ 36.

[120] H. Gall, et al., The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups, *J. Heart Lung Transplant.* 36(9):957-67 (2017) (LIQ_PH-ILD_00001617) ("Gall 2017") at 965; Channick Opening Report at ¶ 36.

[121] Channick Opening Report at ¶¶ 36, 119-157, 217-221; *see also id.* at ¶ 278 (citing Rajeev Saggar Depo. Tr. at 222:13-223:12; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 20:17-21:18; Tapson Depo. Tr. at 40:5-21; Waxman Depo. Tr. at 204:24-205:5, Agarwal 2015 at LIQ_PH-ILD_00148508; Faria-Urbina 2018 at UTC_PH-ILD_009936.)

[122] Channick Opening Report at ¶ 279.

treat patients in WHO groups outside of Group 1, including to treat patients with PH-ILD, as early as 2010:

> Q. Prior to 2014, had you been using Tyvaso off-label for treatment of PH-ILD?
>
> A. Yes, I was.
>
> Q. When was the first time that you can recall that you used Tyvaso off-label for treatment of PH-ILD?
>
> A. On or around 2010.
>
> Q. When you were using Tyvaso off-label to treat PH-ILD before its approval in PH-ILD, what was the dose that you would use in your patients?
>
> A. Nine to 12 breaths, four times a day.
>
> Q. So it's the same dose escalation that's described in the Tyvaso label for PAH; is that correct?
>
> A. Yes. So at the time, Tyvaso was approved in Group 1 PAH. At the time, we believed that the molecule treprostinil would be effective to treat pulmonary hypertension, whether it's Group 1 PAH or it's Group 3 PH-ILD. And so, at that time, given the understanding of how to titrate Tyvaso nebulizer, which was limited, and based on that study, we followed the guidance of that study to help titrate the patient.[123]

Dr. Rajeev Saggar further testified that his brother, Dr. Rajan Saggar, and other physicians—including David Ross, John Belperio, Jeremy Feldman, Shelley Sharpiro, Aaron Waxman, Victor Tapson, Paul Forfia, and Angeli Vavia—used Tyvaso to treat PH-ILD patients before 2020.[124] Dr. Rajan Saggar confirmed during deposition that he used treprostinil to treat patients with PH-ILD as early as 2009.[125] Dr. Rajan Saggar even testified that he had used intravenous treprostinil

[123] Rajeev Saggar Depo. Tr. at 222:13-223:12; *see also* Channick Opening Report at ¶ 279 (citing Rajeev Saggar Depo. Tr. at 49:4-11, 202:8-203:1, 224:16-225:1, 225:14-226:8.
[124] Channick Opening Report at ¶ 279; *see also* Rajeev Saggar Depo. Tr. at 225:14-226:8.
[125] Channick Opening Report at ¶ 279; *see also* Rajan Saggar Sept. 17, 2024 Depo. Tr. at 27:8-24.

(Remodulin) to treat PH-ILD patients as early as 2005,[126] and that he and his group at UCLA used Tyvaso to treat 75 to 100 PH-ILD patients between 2009 and 2020.[127]

128. Furthermore, other physicians—including Drs. Victor Tapson, Parikh, and Aaron Waxman—confirmed that they prescribed inhaled treprostinil off-label to treat PH-ILD patients. Dr. Victor Tapson testified that he treated patients with PH-ILD with Tyvaso® beginning in the 2009 time frame during his time at Duke University Medical Center, and continued to use it after moving to Cedars Sinai.[128] Dr. Parikh, who authored Parikh 2016, testified that he and other clinicians at Duke used Tyvaso to treat PH-ILD patients before 2020.[129] And Dr. Waxman testified that he treated patients with PH-ILD with inhaled treprostinil as soon as it became commercially available.[130] As Tyvaso® was the first inhaled treprostinil to become commercially available, I agree with Dr. Channick that Dr. Waxman's testimony means that Dr. Waxman began using inhaled treprostinil to treat PH-ILD as early as 2009.[131] Even Dr. Nathan acknowledged at deposition that he may have used inhaled treprostinil off-label to treat PH-ILD patients.[132]

129. Based on the testimony and evidence that clinicians had begun to use inhaled treprostinil to treat PH-ILD patients based on the studies that existed as of 2020, I agree with Dr.

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[126] Channick Opening Report at ¶ 230; *see also* Rajan Saggar Sept. 17, 2024 Depo. Tr. at 20:17-21:21.
[127] Channick Opening Report at ¶ 230; *see also* Rajan Saggar Sept. 17, 2024 Depo. Tr. at 143:12-23.
[128] Channick Opening Report at ¶ 282; *see also* Tapson Depo. Tr. at 43:16-44:21 (discussing Tyvaso use for PH-ILD patients at Duke), 52:5-23 (discussing Tyvaso use for PH-ILD patients at Cedars Sinai.)
[129] Channick Opening Report at ¶ 282; *see also* Parikh Depo. Tr. at 23:11-25:11; 33:20-14; *see also below* V.E.2.c ("Dr. Kishan Parikh's Deposition Testimony Shows That POSAs Expected That Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Before 2020").
[130] Channick Opening Report at ¶ 283; *see also* Waxman Depo. Tr. at 49:22-50:5.
[131] Channick Opening Report at ¶ 283.
[132] Channick Opening Report at ¶ 278; *see also* Nathan Depo. Tr. at 88:19-89:21, 92:15-20, 96:6-8.

Channick's opinion that POSAs reasonably expected that inhaled treprostinil could successfully treat PH-ILD.[133] I further understand from Dr. Channick that many physicians measured and saw significant improvements in exercise capacity based on the positive results of the Faria-Urbina 2018 study.[134]

2. The Deposition Testimony of POSAs Provides Further Evidence That POSAs Expected Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Before 2020

a. Dr. Waxman's Deposition Testimony Shows That POSAs Expected That Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Based On Positive Results From Prior Studies Like the Single-Arm Study in Faria-Urbina 2018

130. The deposition testimony of Dr. Waxman, who was one of the authors of Faria-Urbina 2018 and Agarwal 2015, shows that POSAs expected that inhaled treprostinil could be used to successfully treat PH-ILD patients based on the results of pre-2020 studies.[135] Indeed, Dr. Waxman even testified that opponents of using Tyvaso® to treat PH-ILD patients were "narrow minded conservative physicians" who believed "that if you deviate from the guidelines, you aren't doing the right thing."[136] As explained by Dr. Waxman, there were "lots of overlap between the various groups. When you look at the pathology," "the mediators that are circulating," "the fundamental abnormalities of proliferation and abnormal cell death" and that "it made sense, again, in my opinion, to study this drug in other forms of pulmonary hypertension."[137] I understand that this aligns with Dr. Channick's opinion that a POSA would reasonably expect that the positive impact on the hemodynamics of a PAH patient treated with inhaled treprostinil would carry over

[133] Channick Opening Report at ¶ 284.
[134] Channick Opening Report at ¶¶ 36, 278.
[135] Faria-Urbina 2018 at UTC_PH-ILD_009936; *see also* Channick Opening Report ¶ 231.
[136] Waxman Depo. Tr. at 226:11-17; *see also* Channick Opening Report ¶ 28.
[137] Waxman Depo. Tr. at 50:18-51:10; *see also* 2017 Waxman Tr. at 3:17-4:10; *see also* Channick Opening Report ¶ 28.

to PH-ILD patients because there is significant overlap between Groups 1 and Group 3 PH.[138]

131. Dr. Waxman further testified that the single-arm Faria-Urbina 2018 study provided "real world" experience of using inhaled treprostinil to successfully treat PH-ILD patients from at least 2009.[139] Dr. Waxman also testified that outside of the 22 patients in Faria-Urbina 2018, Dr. Waxman and his colleagues continued to use inhaled treprostinil in PH-ILD patients with success.[140]

132. [redacted]

[138] Channick Opening Report at ¶ 231.
[139] Channick Opening Report at ¶ 276; Waxman Depo. Tr. at 95:12-16.
[140] Channick Opening Report at ¶ 276; Waxman Depo. Tr. at 84:20-85:3.
[141] Channick Opening Report at ¶230. I understand that Dr. Waxman was an expert for UTC in an earlier litigation concerning the '793 patent. (*See* Reply Expert Report of Aaron Waxman, M.D., Ph.D. in *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755-RGA (D. Del. Dec. 10, 2021) (LIQ_PH-ILD_00000911) ("Waxman Reply Report").)
[142] Reply Expert Report of Aaron Waxman, M.D., Ph.D. in *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755-RGA (D. Del. Dec. 10, 2021) (LIQ_PH-ILD_00000911) ("Waxman Reply Report") at ¶¶ 22–24; *see also* Channick Opening Report at ¶ 230.
[143] Channick Opening Report at ¶ 230.
[144] I understand from Dr. Channick that the TRIUMPH I study was a 12-week, randomized, double blind, placebo-controlled multi-center study of patients with PAH and measured 6MWD. (*See* Channick Opening Report at ¶ 230).
[145] Channick Opening Report at ¶ 230; Opening Expert Report of Aaron Waxman, M.D. Ph.D., in *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755-RGA (D. Del. Oct. 15, 2021) (LIQ_PH-ILD_00000871) ("Waxman Opening Report") at ¶¶ 73-75; Waxman Reply Report

[redacted] I understand from Dr. Channick that a POSA would have understood that these benefits correlated with an improvement in exercise capacity.[147]

b. Dr. Rajan Saggar's Deposition Testimony Shows That POSAs Expected That Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Based On Positive Results From Pre-2020 Studies Like Saggar 2014 and Agarwal 2015

133. The deposition testimony of Dr. Rajan Saggar, who was one of the authors of Saggar 2014, shows that POSAs expected inhaled treprostinil could be used to successfully treat PH-ILD patients based on positive results of pre-2020 studies like Saggar 2014 and Agarwal 2015. For example, Dr. Rajan Saggar testified that preliminary data published between 2010 and 2016 "supported the concept" that inhaled treprostinil could successfully treat PH-ILD:

> Q. Did -- in your discussions with United Therapeutics and Martine Rothblatt from 2010 to about 2016, did they express any skepticism about the use of inhaled Treprostinil to treat PH-ILD?

(LIQ_PH-ILD_00000911) at ¶ 24; *see also* Waxman IPR Depo. Tr. (LIQ_PH-ILD_00000579) at 40:12-19 ("[I]f I see a hemodynamic improvement, that likely does result in some improvement. Whether it's a subject or physiologic improvement, that may be different, but nonetheless, if a patient has hemodynamic improvement, it's likely that their heart function will improve and I would anticipate that their survival will improve"); 42:14-22 ("[I]f you are talking about a drug that is a vasodilator . . . . if you do see a hemodynamic response that would suggest the drug is effective and is worth pursuing"); 152:1-8 (responding "[n]o" when asked if "[y]ou would agree . . . that some patients may experience improvements in hemodynamics and not see a corresponding change in other nonhemodynamic measures as you've described that apply in the clinic, correct?").

[146] Channick Opening Report at ¶ 230; Waxman Reply Report (LIQ_PH-ILD_00000911) at ¶ 24; Waxman Trial Tr. (LIQ_PH-ILD_00000792) at 651:14-22; *see also id.* at 652:11-653:2; Clark Depo. Tr. at 55:19-56:3 ("[W]hat these molecules do is they cause dilation of the pulmonary vasculature which reduces the pulmonary vascular resistance which reduces the pulmonary artery pressure, and that's a prerequisite to having a long-term clinical benefit.").

[147] Channick Opening Report at ¶ 230.

> A. No. Again, I -- I think our preliminary data here supported the concept that Treprostinil, as a molecule, worked and provided efficacy and a safety profile that was desirable in PH-ILD. I think we all -- we had enough initial data to do a large clinical study. That was very clear.[148]

Dr. Rajan Saggar further testified that he believed that inhaled treprostinil could improve FVC in PH-ILD patients based on the experience and data described in Saggar 2009:

> Q. So you just mention that your belief that treprostinil, including TYVASO, could be used to improve forced vital capacity in PH-ILD patients developed in this 2005 to 2010 time period; is that correct?
>
> A. Correct. I mean with inhaled Treprostinil, experience would have been in the first year after it was approved because I had no experience with inhaled Treprostinil prior to 2009 in this population.[149]

Dr. Rajan Saggar also testified that by 2016, UTC and other clinicians all agreed "that treprostinil itself [] worked in PH-ILD or at least had reasonable amount of data to suggest so."[150]

c. Dr. Kishan Parikh's Deposition Testimony Shows That POSAs Expected That Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Based on Pre-2020 Clinical Experience

134. The deposition testimony of Dr. Kishan Parikh, who was one of the authors of Parikh 2016, shows that POSAs expected inhaled treprostinil could be used to successfully treat PH-ILD patients before 2020. For example, Dr. Parikh testified that he believed inhaled treprostinil (Tyvaso) could be used to treat PH-ILD patients because he began prescribing it to patients by 2018:

> Q. Between 2016 and 2020, did it strengthen your belief that TYVASO could be used to treat PH-ILD patients that had a precapillary component of their disease?

[148] Rajan Saggar Sept. 17, 2024 Depo. Tr. at 97:15 – 98:2.
[149] Rajan Saggar Sept. 17, 2024 Depo. Tr. at 57:10-20.
[150] *See* Rajan Saggar Sept. 17, 2024 Depo. Tr. at 98:7-10.

A. What happened between 2016 and 2020, that would lead to that?

Q. I'm asking you if you personally, if your belief changed during that time period.

A. I suppose so. If -- in 2018 I became an attending, so I was prescribing it, so I felt like -- I must have felt like there was some rationale to do that.[151]

Dr. Parikh further explained that he believed inhaled treprostinil could be used to treat PH-ILD patients based on what he and his colleagues already knew about the "mechanism of action" of inhaled treprostinil before 2020:

Q. Do you believe that the reason that TYVASO is having a treatment effect on at least a subset of PH-ILD patients has to do with its mechanism of action as a vasodilator in those patients?

A. Yes.

Q. Why do you believe that?

A. We selected patients that have the precapillary disease so they have vasoconstriction as part of their pathophysiology. So from what we know about the drug and what we see, that there's some benefit that we would have seen with it as part of it.

Q. And you had that belief prior to 2020, correct --

A. Yes.[152]

d. Dr. Victor Tapson's Deposition Testimony Shows That POSAs Expected That Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Based on Pre-2020 Clinical Experience and Studies Like Agarwal 2015

135. The deposition testimony of Dr. Victor Tapson shows that POSAs expected inhaled treprostinil could be used to successfully treat PH-ILD patients before 2020. As discussed above,

[151] Parikh Depo Tr. at 71:21 – 72:9.
[152] Parikh Depo Tr. at 73:18 – 74:10.

Dr. Tapson had used inhaled treprostinil to treat PH-ILD patients beginning in the 2009 time frame while he was at Duke,[153] and continued to use it after moving to Ceders-Sinai.[154] During his deposition, Dr. Tapson explained that he use inhaled treprostinil to treat PH-ILD patients because it "made intuitive sense" to do so even before 2020:

> Q. Because you had little in the way of drug treatments for these PH-ILD patients, that motivated you to try Tyvaso® in those types of patients, right? To give them something?
>
> A. It made intuitive sense to try it.
>
> Q. What do you mean "intuitive sense"?
>
> A. Well, based on patients have lung disease and delivering a drug directionally to the lung, avoiding some systemic side effects and avoiding VQ mismatch or trying to reduce it, seemed logical.[155]

[redacted]

[153] Channick Opening Report at ¶ 282; *see also* Tapson Depo. Tr. at 43:16-44:21 (discussing Tyvaso use for PH-ILD patients at Duke).
[154] Channick Opening Report at ¶ 282; *see also* Tapson Depo. Tr. at 52:5-23 (discussing Tyvaso use for PH-ILD patients at Cedars Sinai).
[155] Tapson Depo. Tr. at 67:11-24.

[redacted]

e. The Named Inventors' Deposition Testimony Supports That POSAs Expected Inhaled Treprostinil Would Successfully Treat PH-ILD Patients Based on Positive Results From Pre-2020 Studies Like Saggar 2014 and Agarwal 2015

136. The deposition testimony of named inventors Chunqin Deng and Dr. Peter Smith show that POSAs expected inhaled treprostinil could be used to successfully treat PH-ILD patients based on positive results from pre-2020 studies like Saggar 2014 and Agarwal 2015.

137. First, the testimony of Chunqin Deng, a named inventor on the '327 patent, shows that POSAs expected inhaled treprostinil would successfully treat PH-ILD patients based on positive results from Saggar 2014. In relevant part, Chunqin Deng testified that "if you focus on the pulmonary hypertension side, no matter what is underlying disease, if your drug working in the WHO Group 1, there's a reasonable assumption that probably you can test that in other WHO groups: WHO Group 2, WHO Group 3, WHO Group 4, WHO Group 5."[157] From Dr. Channick, I understand this to mean that it would be reasonable for a POSA to expect treprostinil to successfully treat Group 3 PH patients if treprostinil would work at treating Group 1 PAH patients because a POSA would understand that even a different route of administering the same molecule would likely achieve the same results.[158] Therefore, I understand from Dr. Channick and Chunqin Deng that a POSA could look at the results of the single-arm Saggar 2014 study, which treated

[156] Tapson Depo. Tr. at 133:12-135:8 (emphasis added).
[157] Deng Depo. Tr. at 23:5-24:11; *id.* at 23:22-24:5; *see also* Channick Opening Report at ¶¶ 28, 116.
[158] Channick Opening Report at ¶ 116.

Group 1 PAH patients with parenteral treprostinil, and reasonably infer that inhaled treprostinil could successfully treat Group 3 PH patients.[159]

[redacted]

[159] Channick Opening Report at ¶¶ 28, 116.
[159] Channick Opening Report at ¶ 116.
[160] Smith Depo. Tr. at 48:5-17, 49:8-16; *see also* Channick Opening Report ¶ 37; 2015 Waxman Presentation (UTC_PH-ILD_082484).
[161] Channick Opening Report at ¶ 37; *see also* Waxman Depo. Tr. at 46:22-47:4; 47:17-22.

[redacted]

3. Public Presentations Concerning Pre-2020 Studies Show That POSAs Expected That Inhaled Treprostinil Could Be Used to Successfully Treat PH-ILD Patients

a. The 2017 Recruitment Presentation (Faria-Urbina 2018 and Agarwal 2015)

139. I understand that the 2017 Recruitment Presentation, entitled "Tyvaso in Pulmonary Hypertension Due to Interstitial Lung Disease (PH-ILD): The INCREASE Study," was provided to the INCREASE steering committee members so that they could publicly share the presentation with other physicians.[164] I further understand that the third slide of the 2017 Recruitment Presentation, titled "Supportive Evidence for Tyvaso in WHO Group 3 PH," refers to that data presented in Agarwal 2015.[165] Other slides from the 2017 Recruitment Presentation discuss Dr. Waxman's data.[166] Specifically, the "Discussion and Conclusion" slide states that "this study provides preliminary evidence supporting the safety and efficacy of inhaled treprostinil in the treatment of Group 3 PH with advanced lung disease complicated by pulmonary vascular remodeling."[167] Accordingly, I agree with Dr. Channick's opinion that the 2017 Recruitment

[162] *See* Channick Opening Report at ¶ 37; A. Waxman email to Dr. Gil Golden (Oct. 21, 2014) (UTC_LIQ00161733) at UTC_LIQ_00161735.)
[163] Channick Opening Report at ¶ 37.
[164] Channick Opening Report at ¶ 270; 2017 Recruitment Presentation (UTC_PH-ILD_081749); *see also* 2017 Email UTC_PH-ILD_081748; Smith Depo. Tr. at 158:11-160:6.; Tapson Depo. Tr. at 130:5-131:17.
[165] 2017 Recruitment Presentation at UTC_PH-ILD_081752; Channick Opening Report at ¶ 270.
[166] 2017 Recruitment Presentation at UTC_PH-ILD_081755; Channick Opening Report at ¶ 270.
[167] *Id.*

Presentation confirms that a POSA would reasonably expect to be successful with improving exercise capacity in PH-ILD patients using inhaled treprostinil based on the data in Faria-Urbina 2018 and Agarwal 2015.[168]

b. The Waxman 2017 Presentation (Faria-Urbina 2018)

140. I understand that on March 17, 2017, Dr. Waxman gave a presentation at the 12th Annual John Vain Memorial Symposium on the topic "Is There a Therapeutic Opportunity for Prostacyclins in Patients with PH Secondary to Primary Pulmonary Disease" (the "Waxman 2017 Presentation").[169] The presentation was recorded and publicly shared on Vimeo as of May 22, 2017.[170]

141. I further understand that during the presentation, Dr. Waxman described the rationale and findings of the same study that was eventually published in Faria-Urbina 2018.[171] Dr. Waxman explained that the rationale was based on the understanding that "treatment directed at pulmonary remodeling should potentially benefit any patient with a form of pulmonary vascular disease" and that "pathways that are active in patients with PAH are also active in patients with Group 3 and even Group 2 and Group 3 and even Group 5 [patients]."[172] Accordingly, he and the other authors of Faria-Urbina 2018 "decided to prospectively treat patients and do a retrospective

[168] Channick Opening Report at ¶ 270.
[169] 2017 Waxman Tr. at LIQ_PH-ILD_00147328; see also Waxman Depo. Tr. at 70:14-93:14.
[170] A. Waxman, "Is there a therapeutic opportunity for prostacyclins in patients with pulmonary hypertension secondary to primary pulmonary disease?", 12th Annual John Vain Memorial Symposium, March 17, 2017, https://vimeo.com/218433991/157aa6fb84?share=copy (LIQ_PH-ILD_00147322) ("2017 Waxman Presentation"); A. Waxman, "Is there a therapeutic opportunity for prostacyclins in patients with pulmonary hypertension secondary to primary pulmonary disease?", 12th Annual John Vain Memorial Symposium, March 17, 2017 ("2017 Waxman Tr.") (LIQ_PH-ILD_00147328); *see id.* at LIQ_PH-ILD_00147330 ("So the treatment directed at pulmonary vascular remodeling should potentially benefit any patient with a form of pulmonary vascular disease.").
[171] Channick Opening Report at ¶¶ 120, 272-273; *see also* Waxman Depo. Tr. at 68:18-73:13, 93:98-14.
[172] 2017 Waxman Tr. at 3:4-7; 3:20-22; *see also id.* at 73:1-77:17.

analysis of that data."[173] Dr. Waxman then discussed the data from the study that would eventually be published in Faria-Urbina 2018.[174] He concluded the presentation by stating:

> And so to finish up, hopefully, you'll agree that at least these pilot findings do provide some support -- additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And that these findings also provide additional evidence supporting more at – larger clinical trials in patients with this form of pulmonary vascular disease.[175]

142. In view of Dr. Waxman's statements that the same data contained in the Faria-Urbina 2018 study provided "additional support" for using Tyvaso in "the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease," I agree with Dr. Channick's opinion that the single-arm Faria-Urbina 2018 study would have given POSAs a reasonable expectation of successfully treating PH-ILD patients, including improving their exercise capacity with inhaled treprostinil.[176]

c. Dr. Waxman's 2018 UTC Science Day Presentation (Faria-Urbina 2018)

143. I understand that in 2018, Dr. Waxman gave a presentation titled "The iTRE Study Therapeutic Opportunity for Inhaled Treprostinil in Patients with PH Secondary to Primary Pulmonary Vascular Disease" (the "Waxman 2018 Presentation").[177] I understand that this presentation publicly delivered at UTC's 2018 Science Day.[178]

144. Starting at the slide labeled LIQ_PH_ILD_00101311, the Waxman 2018 Presentation references the Faria-Urbina 2018 study and describes the retroactive study before

[173] 2017 Waxman Tr. at 7:16-9:7; *see also* Waxman Depo. Tr. at 80:6-81:10.
[174] Waxman Depo. Tr. at 68-93.
[175] Waxman Depo. Tr. at 91:7-13; 2017 Waxman Tr. at 17:8-16.
[176] Channick Opening Report at ¶ 272.
[177] Channick Opening Report at ¶ 274; 2018 Waxman Presentation (LIQ_PH-ILD_00101301).
[178] Channick Opening Report at ¶ 274; Waxman Depo. Tr. 118:14-119:18.

concluding that "[t]he findings of this pilot study provide preliminary evidence supporting the treatment of pre-capillary PH in patients with advanced lung disease."[179] Based on these slides, I understand from Dr. Channick that the Faria-Urbina 2018 study would have given a POSA a reasonable expectation of success with using inhaled treprostinil to treat PH-ILD and improve their exercise capacity.[180]

4. UTC's Documents Show That a POSA Would Have a Reasonable Expectation of Successfully Improving Exercise Capacity in PH-ILD Patients Before 2020

a. [redacted]

145. [redacted]

b. [redacted]

146. [redacted]

[179] *See* 2018 Waxman Presentation at LIQ_PH-ILD_00101311–316.
[180] Channick Opening Report at ¶ 274.
[181] Channick Opening Report at ¶ 286; A. Waxman's letter re Orphan Drug Designation to the FDA (November 15, 2017) (UTC_LIQ00104555) at UTC_LIQ00104556 (emphasis added).
[182] Channick Opening Report at ¶ 286; Waxman Depo. Tr. at 186:6-10.
[183] A. Waxman's letter re Orphan Drug Designation to the FDA (November 15, 2017) (UTC_LIQ00104555) at UTC_LIQ00104556 (emphasis added).
[184] Channick Opening Report at ¶¶ 286-287.

[redacted][187]

5. Statements Of UTC's Chairman and CEO Supporting Reasonable Expectation of Success

147. Further supporting the use of inhaled treprostinil to treat PH-ILD are the public statements of UTC's Chairman and CEO, Dr. Martine Rothblatt, made during UTC's May 2, 2018 earnings call for Q1 2018. These statements also illustrate that UTC pursued the INCREASE Study based on the positive results from pre-2020 studies. I understand that when asked about the rationale behind using Tyvaso in ILD during the call,[188] Dr. Rothblatt responded:

> [S]tarting with the COPD and ILD. Treprostinil, Tyvaso is not on label for patients with these indications. And as you would expect, it's not an inexpensive therapy, and patients don't just, like, blindly push the pay button on Tyvaso. Every patient is carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient. Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. ***I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works."*** In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved ***So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters***, we went ahead and then had the statistics to power of the study for statistical

[185] Channick Opening Report at ¶ 289; *see also* UTC_WAT00628950-628951.
[186] UTC_WAT00628950-628951.
[187] Channick Opening Report at ¶ 289.
[188] Channick Opening Report at ¶ 267; UTC 2018 Earnings Call at LIQ_PH-ILD_00000009.

> significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.[189]

148. As noted in the context of the quote above, Dr. Rothblatt stated publicly in 2018, in the context of an investor earnings call that "this drug works," attributing that statement to known expert clinician Dr. Waxman. This discussion was also specifically in the context of ILD and WHO Group III, as noted in the quoted language above.

F. Treprostinil Clinical Studies in PH-ILD Patients

1. The INCREASE Study

149. I understand that the INCREASE Study was multicenter, randomized, double-blind, placebo-controlled trial prepared and conducted by UTC.[190] The INCREASE Study Protocol, titled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease," is dated October 21, 2015.[191] The final amendment to the INCREASE study protocol was February 15, 2017.[192]

150. The results of the INCREASE Study were reported in an article titled "Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease" (the "Waxman 2021" article), which was published in the *New England Journal of Medicine* on January 13, 2021.[193] Patient characteristics were summarized in Table 1 of Waxman 2021, which included the "Cause of Lung Disease" for the 326 patients that were part of the INCREASE Study:[194]

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[189] Channick Opening Report at ¶ 266; UTC 2018 Earnings Call at LIQ_PH-ILD_00000009 (emphasis added).
[190] Waxman et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease,* 384 N. Engl. J. Med. 325 (2023) ("Waxman 2021") (LIQ_PH-ILD_00122745).
[191] *See* UTC_PH-ILD_054882 ("Original Protocol").
[192] *See* UTC_PH-ILD_105083 ("Final Protocol") (showing that the date of the final amendment of the INCREASE study protocol is February 15, 2017.)
[193] Waxman 2021 at LIQ_PH-ILD_00122745.
[194] *Id.* at LIQ_PH-ILD_00122750.

Table 1. **Characteristics of the Patients at Baseline.***

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen — no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy — no. (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

151. Figure 1 from Waxman 2021 is a diagram representation of the screening, randomization, and follow-up process for the INCREASE Study:[195]

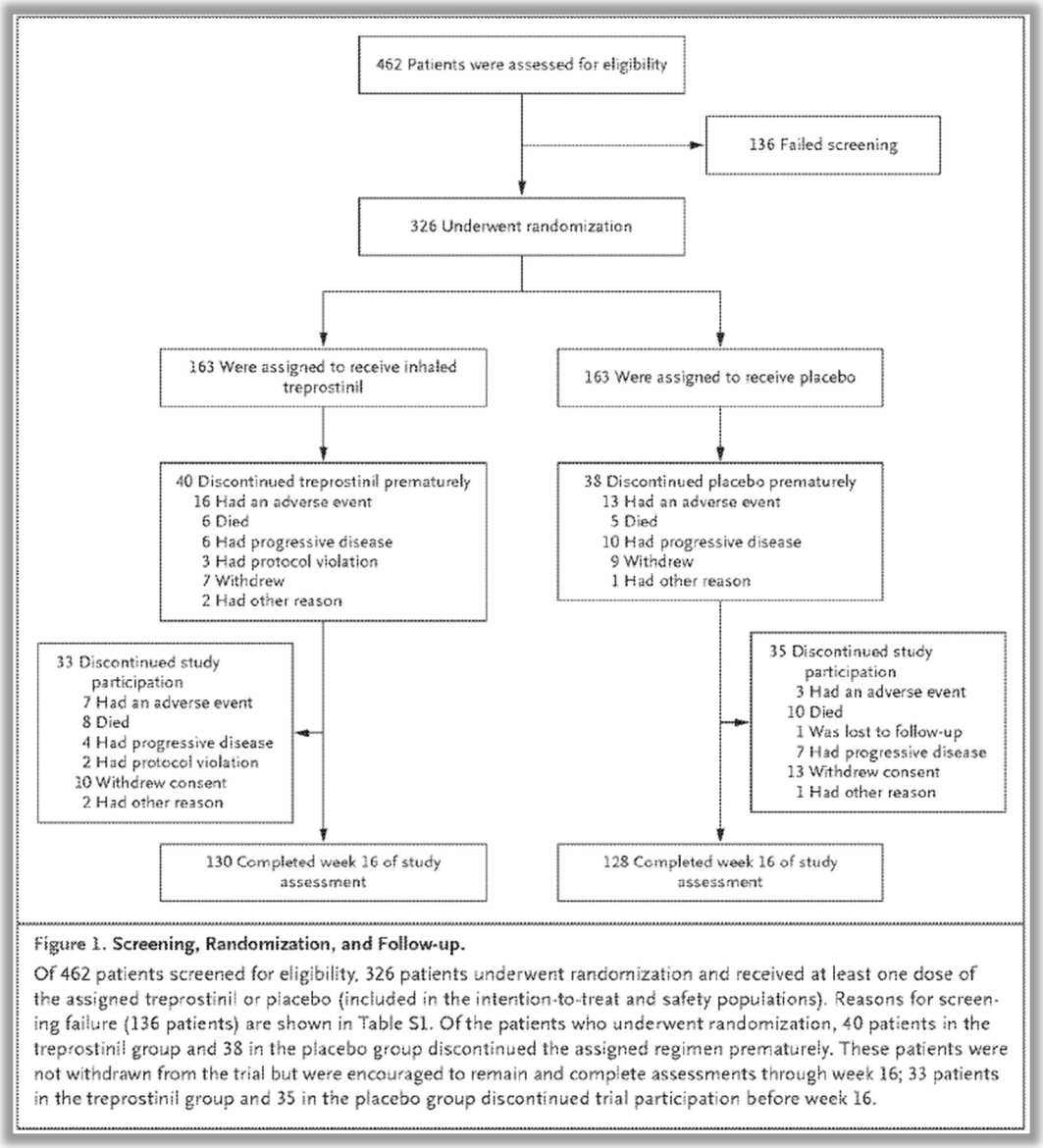

Figure 1. Screening, Randomization, and Follow-up.

Of 462 patients screened for eligibility, 326 patients underwent randomization and received at least one dose of the assigned treprostinil or placebo (included in the intention-to-treat and safety populations). Reasons for screening failure (136 patients) are shown in Table S1. Of the patients who underwent randomization, 40 patients in the treprostinil group and 38 in the placebo group discontinued the assigned regimen prematurely. These patients were not withdrawn from the trial but were encouraged to remain and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued trial participation before week 16.

[195] *Id.* at LIQ_PH-ILD_00122749.

152. As shown below, the Abstract from the Waxman 2021 article summarizes the results of INCREASE Study with respect to patient 6MWD, NT-proBNP levels from baseline, and clinical worsening:[196]

> RESULTS
> A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

Table 2 from the Waxman 2021 article provides the full summary of results for primary and secondary endpoints from the INCREASE Study:[197]

[196] *Id.* at LIQ_PH-ILD_00122745.
[197] *Id.* at LIQ_PH-ILD_00122752.

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

* Plus–minus values are means ±SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.

† The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.

‡ This is a least-squares mean difference between the groups.

§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.

¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.

‖ This is the treatment ratio, which is the ratio of ratios between two treatment groups.

** This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

†† The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

153. I further understand that the INCREASE Study cited several of the studies Dr. Channick identified as relevant to the '327 patent, and explained:

> Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension. Therefore, the

> objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with [PH-ILD].198

154. As noted by Dr. Channick, the INCREASE Study's reference to "previously completed pilot studies" included the Faria-Urbina 2018 and Agarwal 2015 studies summarized above.[199]

a. UTC Documents Show That UTC Pursued the INCREASE Study Based On The Positive Results From Pre-2020 Studies Using Treprostinil to Treat PH Patients

155. I understand from Dr. Channick that data in Agarwal 2015 was cited as the one the studies that formed the rationale for pursuing the INCREASE Study.[200] The INCREASE Study Protocol section titled "Rationale For Development of Study Drug in Disease/Condition" describes the rationale for using inhaled treprostinil to treat patients with PH-ILD, and specifies that "[i]nhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity."[201]

156. [redacted]

[redacted]

[redacted]

198 NEJM Publication at UTC_PH-ILD_010791 (citing Agarwal 2015, Faria-Urbina 2018, L. Wang, et al., Hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension, *Int'l J. COPD*, 12:3353-60 (2017) (UTC_PH-ILD_010782), and A. Bajwa, et al., The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease, *Pulmonary Circulation* 7:82-88 (2017) (UTC_PH-ILD_009846); Channick Opening Report at ¶ 38.

199 NEJM Publication at UTC_PH-ILD_010791; Channick Opening Report at ¶ 261.

200 Waxman Depo. Tr.at 169:1-11; Channick Opening Report at ¶ 261.

201 *See* Original Protocol at UTC_PH-ILD_054899; Final Protocol at UTC_PH-ILD-105100. Channick Opening Report at ¶ 261.

202 Channick Opening Report at ¶ 264; Investigator Brochure (UTC_PH-ILD_082805) at UTC_PH-ILD_082814.

[redacted]

157. [redacted]

b. The Statements Of UTC's Chairman and CEO Show That UTC Pursued the INCREASE Study Based On The Positive Results From Pre-2020 Studies Using Treprostinil to Treat PH Patients

158. As I noted above in Section V.E.5, the public statements of UTC's Chairman and CEO, Dr. Martine Rothblatt, made during UTC's May 2, 2018 earnings call for Q1 2018 further shows that UTC pursued the INCREASE Study based on the positive results from pre-2020 studies. I understand that when asked about the rationale behind using Tyvaso in ILD during the call,[207] Dr. Rothblatt responded:

> [S]tarting with the COPD and ILD. Treprostinil, Tyvaso is not on label for patients with these indications. And as you would expect, it's not an inexpensive therapy, and payers don't just, like, blindly push the pay button on Tyvaso. Every patient is carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient. Having said that, both through

[203] Channick Opening Report at ¶ 264; Investigator's brochure at UTC_PH-ILD_082813.
[204] I understand that Dr. Tapson was a member of the INCREASE steering committee. Channick Opening Report at ¶ 264; Tapson Depo. Tr. at 80:12-19.
[205] Channick Opening Report at ¶ 264; Tapson Depo. Tr. at 80:12-19, 84:7-85:1.
[206] Channick Opening Report at ¶ 264; Investigator's brochure at UTC_PH-ILD_082813; Tapson Depo. Tr. at 94:7-25.
[207] Channick Opening Report at ¶ 267; UTC 2018 Earnings Call at LIQ_PH-ILD_00000009.

> the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. ***I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works."*** In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved ***So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters***, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.[208]

159. I agree with Dr. Channick's opinion that Dr. Rothblatt's above-statements suggest that Dr. Waxman treated PH-ILD patients with Tyvaso before the earnings call on May 2, 2018.[209] I further agree with Dr. Channick's opinion that Dr. Rothblatt's statement about having seen "posters" and "publications" with data on using Tyvaso to treat PH-ILD patients is an acknowledgment of Faria-Urbina 2018 and Agarwal 2015 because both studies speak directly to using Tyvaso to treat PH-ILD patients.[210]

2. The PERFECT Study

160. I understand the PERFECT Study was a multi-center, randomized, double-blind, placebo-controlled, 12-week crossover trial of inhaled treprostinil to treat PH-COPD.[211] I further understand that the PERFECT Study was discussed in the article titled "Inhaled Treprostinil in Pulmonary Hypertension Associated with COPD: PERFECT Study Results" (the "Nathan 2024"

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[208] Channick Opening Report at ¶ 267; UTC 2018 Earnings Call at LIQ_PH-ILD_00000009 (emphasis added).
[209] Channick Opening Report at ¶ 267;
[210] Channick Opening Report at ¶ 267;
[211] Thisted Rebuttal Report at ¶ 206; Steven D. Nathan et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with COPD: PERFECT Study Results*, 63 Eur. Respiratory J. (2024) ("Nathan 2024") (produced as document starting at UTC_PH-ILD_227135)

article).[212]

161. Based on Nathan 2024 and the Thisted Report, I further understand that the study was terminated as of September 2022, before it was completed.[213] As a result of the termination of the PERFECT trial, the clinical observations and other details of the PERFECT trial could not be known to a POSA in 2020 or 2021. The study was terminated because patients who received inhaled treprostinil a greater rate of serious adverse events than placebo groups, including events that lead to hospitalization.[214] These results are discussed in Table 3 of the Nathan 2024 article:[215]

TABLE 3 Treatment-emergent adverse events (TEAEs): safety population

	Enrolled	Randomised	
	iTRE (run-in) (n=108)	iTRE* (blinded) (n=66)	Placebo (blinded) (n=58)
Total TEAEs	165	178	122
Subjects with ⩾1 TEAEs	67 (62.0)	47 (71.2)	38 (65.5)
SAEs	10	26	20
Subjects with ⩾1 SAEs	9 (8.3)	17 (25.8)	6 (10.3)
TEAEs related to study treatment	115	77	32
Subjects with ⩾1 TEAEs related to study treatment	48 (44.4)	29 (43.9)	15 (25.9)
TEAEs leading to treatment discontinuation	15	11	6
Subjects with ⩾1 TEAEs leading to treatment discontinuation	11 (10.2)	8 (12.1)	3 (5.2)
TEAEs leading to study discontinuation	24	14	12
Subjects with ⩾1 TEAEs leading to study discontinuation	16 (14.8)	10 (15.2)	2 (3.4)

Data are presented as n or n (%). iTRE: inhaled treprostinil; SAE: serious adverse event. *: number of subjects exposed to iTRE during 12-week blinded treatment period only, including washout period.

162. In his discussion of the Nathan 2024 article discussing the PERFECT study, Dr. Thisted notably emphasizes his belief that the study "showed no improvement on 6MWD when compared with placebo," and appears to imply that the PERFECT study thus shows that inhaled treprostinil was not an effective treatment for improving exercise capacity compared to placebo.

[212] Nathan 2024 at UTC_PH-ILD_227136.
[213] Thisted Rebuttal Report at ¶ 207.
[214] Nathan 2024 at UTC_PH-ILD_227140.
[215] Nathan 2024 at UTC_PH-ILD_227142 (Table 3).

Dr. Thisted omits from his report, however, the fact that the Nathan 2024 did not perform any statistical analysis on efficacy measures like 6MWD, "due to the early study termination and lack of appropriate sample size."[216] Under Dr. Thisted's repeated mantra that a POSA cannot draw any inferences at all from clinical trials that are not large, randomized clinical trials, it is not actually possible to draw the conclusion that treprostinil failed to improve 6MWD as Dr. Thisted appears to imply. To the extent Dr. Thisted intended this implication, I find it notable that Dr. Thisted is apparently happy to rely on small sample size data, without statistical significance, if that data happens to support his opinions rebutting Drs. Channick and Hill.

VI. DR. THISTED'S OPINIONS CRITIQUING DR. CHANNICK'S ANALYIS OF THE PRIOR ART AND THE INCREASE STUDY

163. In ¶¶ 212-259 of his report, Dr. Thisted provides several critiques of Dr. Channick's opinions as they pertain to the INCREASE study and the prior art references Dr. Channick relies on for his opinions on anticipation and obviousness. I respond to Dr. Thisted's critiques in this section.

164. At a high level, Dr. Thisted's essential criticism of Dr. Channick's opinions boils down to Dr. Thisted's assertion that single-arm studies cannot tell a POSA anything *at all* about the effectiveness of a drug regimen. Throughout his report Dr. Thisted opines that a POSA cannot draw any inferences whatsoever about efficacy from patient change scores in single arm studies. For example, Dr. Thisted's core opinion is embodied in his statement that "tests of statistical significance in change scores in patients, all of whom have received the same treatment under study—here, inhaled treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment." (*See, e.g.* Thisted Rpt., ¶ 154 (emphasis added).) Dr. Thisted repeats this phrase as a kind of mantra several times throughout his report. (*See id.,* ¶¶ 133, 134, 171, 188, 198, 219,

[216] Nathan 2024 at UTC_PH-ILD_227139.

228, 236, 244, 269, 302.)

165. As I explain in this report, I disagree with Dr. Thisted's core opinion and note that it is contradicted by the behavior of clinical drug developers, both in general and specifically in the case of treprostinil clinical development. It is simply not the case that a POSA can draw no inferences whatsoever from single-arm studies. On the contrary, POSAs routinely draw inferences, with an appropriate confidence level, based on single arm and retrospective studies. As indeed they often must, since during the early stages of drug development, uncontrolled clinical reports may be the only evidence of efficacy available to a POSA who must make decisions about whether and how to treat a patient "off-label." And in some cases, such as with treprostinil in the context of the specific method of treatment claimed by the '327 patent, such single-arm derived efficacy signal can be sufficient for a POSA to have a reasonable expectation of success that the treatment will work.

166. Relatedly, much of Dr. Thisted's report is directed toward the level of evidence that is usually required to obtain FDA approval for use of a new drug in humans. But examination of this analysis answers the wrong question. As noted in the discussion of legal standards above, the level of evidence/certainty typically required for FDA approval is greater than the level of evidence/certainty generally considered sufficient in the context of the patent law concept of a "reasonable expectation of success." Accordingly, the main issue under consideration here is whether the claims of the '327 patent are anticipated and/or obvious in view of the prior art. In that context, I understand from counsel that the proper question to ask is whether the available data would provide a POSA with a reasonable expectation that use of treprostinil in the manner that is recited in the '327 patent claims would be successful. As I explain in this report, in the context of the facts relevant to this case, the prior art provided more than sufficient data to support a

reasonable expectation of success.[217]

A. Response to Dr. Thisted's Criticisms of Dr. Channick's Analysis of the INCREASE Study

167. In ¶¶ 212-217, Dr. Thisted takes issue with Dr. Channick's discussion of the INCREASE study, and I respond to those critiques here.

168. First, in his discussion of statistical power, I believe Dr. Thisted misinterprets Dr. Channick's statement that "[s]tatistical significance is a matter of adequately powering a study with a sufficient number [of] patients," when Dr. Thisted responds that Dr. Channick is "wrong" that statistical power is solely a matter of sample size. Reviewing Dr. Channick's opinions in context, it appears to me that Dr. Channick was not claiming that the only relevant factor for statistical power is sample size, but rather making the uncontroversial point that statistical power is generally increased when larger numbers of samples are evaluated. Indeed, it appears that Dr. Thisted agrees with this basic point, since he opines that "[r]oughly speaking, a large clinical study has greater power to detect differences than a small clinical study." (*See* Thisted Rpt., ¶ 91.)

169. Beyond this, Dr. Thisted rehashes his point that Faria-Urbina 2018 and Agarwal 2015 report single arm results while INCREASE included a placebo control. Dr. Thisted also contends that the statistical tests used in the different studies would be different, due to the differences in study design. But this misses the point, in my opinion. The issue at hand is whether Dr. Channick is correct that a POSA would expect statistical significance in larger size studies, given that Faria-Urbina 2018 and Agarwal 2015 had already expressly disclosed a statistically significant improvement in 6MWD scores. Indeed, I note that Dr. Thisted does not dispute that Faria-Urbina disclosed a statistically significant improvement in 6MWD scores. (*See* Thisted Rpt., ¶ 244, *see also id.* ¶ 236 (acknowledging statistically significant result disclosed in Agarwal

[217] *See also* Section VIII.A, below

2015).)

170. Even more to the point, Dr. Thisted never explains why it could matter that different tests for statistical significance can be appropriate for use with different types of clinical trial designs. To the extent that some of the claims of the '327 patent recite statistical significance as a claim limitation, none of these claims demand the use of any specific statistical test, nor do they require statistical significance *only as shown by a large randomized clinical trial*. In other words, Dr. Thisted again appears to be evaluating the question of obviousness and reasonable expectation of success, insisting on Phase III clinical trial data when the law (and the claims at issue here) do not require it.

171. Dr. Thisted also takes issue with Dr. Channick's opinion that statistical significance would be obvious in light of the known fact that clinicians such as Dr. Waxman were already seeing benefits in PH-ILD patients with inhaled treprostinil. (Thisted Rpt. ¶ 215.) But Dr. Thisted's opinions in this regard merely restate his overall opinion that he does not consider the statistically significant data reported in Faria-Urbina 2018 and Agarwal 2015 to be evidence for drawing any inferences, at all, about efficacy. As I explain throughout this report, I disagree. I also agree with Dr. Channick that the existence of statistically significant improvement in 6MWD change scores in Agarwal 2015 and Faria-Urbina 2018 would give a POSA a reasonable expectation that the INCREASE trial, which studied the same drug in the same disease and using the same efficacy endpoint, would also be successful in achieving a statistically significant endpoint. Dr. Thisted observes that success of the INCREASE trial was not guaranteed just because of the results of the Faria-Urbina 2018 and Agarwal 2015 studies, but that applies the incorrect legal standard: an assurance or guarantee of success is not required.[218]

[218] *See also* Section VIII.A, below.

172. Finally, I note that Dr. Thisted again reverts to relying on the irrelevant PERFECT clinical trial, which as I have explained is not relevant to the question of reasonable expectation of success. (*See* Section VIII.B.)

B. Response to Dr. Thisted's Criticisms of Dr. Channick's Analysis of the Prior Art

173. In ¶¶ 218-259, Dr. Thisted accuses Dr. Channick of "mischaracterizing" aspects of the prior art publications Saggar 2014, Parikh 2016, Agarwal 2015, and Faria-Urbina 2018. I respond to Dr. Thisted's opinions below.

174. I also note as a general matter that Dr. Thisted's approach attacks each piece of prior art in isolation, and fails to consider the collective whole of the prior art's teachings, which is what a POSA in 2020 would consider in assessing a reasonable expectation of success. For example, Dr. Thisted isolates individual references and argues that each reference, in isolation, would fail to support a POSA's reasonable expectation of success that inhaled treprostinil would successfully improve exercise capacity in PH-ILD patients. As I explain below, I disagree with Dr. Thisted as to his analysis of each of the prior art references. But I further believe that Dr. Thisted's opinions are further flawed for the additional reason that he fails to account for the *collective* weight of all the teachings of the prior art, which he should have done in the context of assessing obviousness and a reasonable expectation of success.

1. Saggar 2014

175. In the case of Saggar 2014, Dr. Thisted says that Dr. Channick "fails to acknowledge" that Saggar 2014 is a single arm study, but I do not see how that is the case – Dr. Channick's report accurately describes the results of the single arm Saggar 2014 study, and does not claim that it is anything other than a single arm study.[219] Notably, however, Dr. Thisted fails

[219] *See* Channick Opening Report at ¶¶ 30, 114-18, 306-16.

to identify any single instance where Dr. Channick did not accurately describe the disclosures of the Saggar 2014 study, and notably Dr. Thisted never disputes that Saggar 2014 does indeed expressly disclose a statistically significant improvement in 6MWD in patients treated with parenteral treprostinil. (*See* Thisted Rpt., ¶ 219.) Instead, Dr. Thisted again focuses on his repeated critique that a single arm study like Saggar 2014 is "not equivalent to *demonstrating* that treprostinil has a treatment effect." (*Id.* (emphasis added; *see also id.*, ¶ 221 ("the data Saggar 2014 reports fail to demonstrate…").) Once again, Dr. Thisted uses the wrong legal standard when he insists that a reasonable expectation of success can exist only when the prior art has already "demonstrated" that a treatment is effective. But the correct legal standard requires only that the prior art support a reasonable expectation of success.[220] Thus, Dr. Thisted's real opinion does not appear to be that Dr. Channick is "mischaracterizing" anything, but rather than he simply disagrees with Dr. Channick that single arm studies can support a reasonable expectation of success.

176. In ¶ 223, Dr. Thisted contends that Dr. Channick failed to account for supposed "bias" in the Saggar 2014 study, and focuses his criticisms on various subjective measures. Dr. Thisted fails to mention in this discussion, however, that 6MWD which Dr. Channick primarily relies on is an objective measure that is not subject to the concerns of subjective bias that Dr. Thisted focuses on. Dr. Thisted's remaining opinions as to bias, such as that the study side showed "selection bias" in choosing its samples size, are entirely speculative and unsupported by any evidence that such bias actually exists. Finally, even if credited, the fact that Saggar 2014 involved 15 patients evaluated in an open label setting would be understood by a POSA and would not prevent a POSA from placing appropriate weight on the persuasiveness of the data reported. In other words, even assuming Dr. Thisted's concerns about bias are fully valid, that would not cause

[220] *See also* Section VIII.A, below.

a POSA to completely discount the statistically significant reported results in the reference, as Dr. Thisted appears to do.

177. Next, Dr. Thisted takes issue with Dr. Channick's opinion that the 1% change in predicted FVC reported in Saggar 2014 is "comparable" to the % change later reported in the INCREASE study. (Thisted Rpt., ¶¶ 224-225.) As an initial matter, I do not see any flaw in Dr. Channick's simple point that the magnitude of the FVC improvement reported in Saggar 2014 (1%) is very similar to the FVC improvement in the treprostinil treatment group in the INCREASE study (1.07%). (*See* Thisted Rpt., ¶ 225.) Secondly, I do not understand that Dr. Channick is arguing that a statistically significant result in one study necessarily means that statistical significance would be achieved in a different study. Instead, I understand that Dr. Channick is opining that a POSA would have a reasonable expectation of success that the 1% FVC improvement reported in Saggar 2014 would be statistically significant if studied in a larger trial with a larger sample size and otherwise similar conditions. Dr. Thisted again opines that the Saggar 2014 study would not provide a guarantee that such a result would be obtained, but the correct legal standard does not demand that much. All that is necessary is that a POSA would have a reasonable expectation of success. I do not see any reason why Dr. Channick's opinion that a POSA would have such an expectation is flawed. I also note the contradiction with Dr. Wertheim's report, discussed below in Section XI, that Dr. Wertheim goes so far as to argue a statistically significant result in one category of result (FVC) is sufficient to simply assume that a statistically significant result in a completely different category of result (6MWD) would be obtained.

178. Finally, in ¶ 226 of his report Dr. Thisted discusses how a POSA would interpret the FVC improvement data in Saggar 2014, and the deposition testimony from Dr. Saggar himself. Dr. Channick and Dr. Saggar rely on the Appendix data reported in Saggar 2014, which does show

that 10 out of 15 patients in the study had an improvement in % predicted FVC at 12 weeks.[221] This means that twice as many patients in the study had improved % predicted FVC than those that did not. On this basis, Dr. Channick concludes that a POSA would have been motivated to combine these teachings from Saggar 2014 with other prior art (Faria-Urbina 2018 and the '793) patent to arrive at the subject matter recited in claims 4-5 of the '327 patent. Dr. Thisted disagrees, but I note in this regard that Dr. Thisted is not a clinician, and is not a POSA, and thus does not have the appropriate clinical training to opine on whether these data would motivate a POSA. I further note that Dr. Thisted focuses on the lack of statistical significance of the data from Saggar 2014 and says the result could "easily be due to chance." I do not know why Dr. Thisted says that this could "easily" be so – Dr. Thisted cannot know the likelihood that this result was in fact due to chance, or that it was "easily" or more likely to be due to chance.

2. Parikh 2016

179. In the case of Parikh 2016, Dr. Thisted again accused Dr. Channick of "mischaracterizing" the results and disclosures of the reference, but I do not see any mischaracterization. Instead, Dr. Channick's report accurately summarizes and reports that Parikh 2016 reported an improvement in 6MWD in a cohort of Group 3 PH patients, several of which (at least 6) had PH-ILD specifically.[222] As with Saggar 2014, Dr. Thisted's real contention is that he disagrees with Dr. Thisted's interpretation of the impact Parikh 2016 would have on a POSA's reasonable expectation of success, not that Dr. Channick is mischaracterizing the disclosures of the reference. For example, Dr. Thisted complains that Parikh 2016 did not specifically report PH-ILD patient efficacy results, instead providing results for the group as a whole, but again Dr. Channick's report accurately describes this. Dr. Thisted simply assumes without evidence that

[221] *See* Channick Opening Report at ¶¶ 310-311; *see also* Saggar 2014 at LIQ_PH-ILD_00000243.
[222] *See* Channick Opening Report at ¶¶ 256-259.

there was "severe selection bias" and that the reported results "do not represent PH-ILD patients," but this is speculation on his part. For example, Dr. Thisted does not identify any evidence that there was, in fact, selection bias in the way patients were selected for analysis in the study. Likewise, he does not identify any evidence to support that the patient results reported were, in fact, unrepresentative of PH-ILD patients.

180. Furthermore, I disagree with Dr. Thisted's statement that Parikh 2016 "fails to disclose any successful efficacy results." (Thisted Rpt., ¶ 229.) This statement can only be understood through the lens of Dr. Thisted's opinion, stated in ¶ 228, that no inferences whatsoever can be drawn from Parikh 2016 because it is a single-arm chart review. I disagree with this because a POSA can (and did, as I discuss below) draw the inference that this study was supportive of the efficacy of inhaled treprostinil in Group 3 PH patients, including PH-ILD patients. As discussed throughout this report, I disagree with Dr. Thisted's opinion that single-arm clinical reports in the prior art would have been completely and entirely discounted by a POSA, as if they did not exist. Once again, Dr. Thisted applies the wrong legal standard when he opines that Parikh's results "fail to demonstrate" efficacy. (Thisted Rpt., ¶ 232.) The correct legal standard is a reasonable expectation of success, not a guarantee that would require that the prior art had already "demonstrated" efficacy.[223]

181. In ¶ 232-233 Dr. Thisted questions whether the results in Parikh 2016 "represent" PH-ILD patients. Dr. Thisted's criticisms are based on unsupported assumptions, such as Dr. Thisted's assumption that the reported 6MWD scores were "inflated," as a matter of fact, simply because some patients discontinued the study due to issues such as the need for more aggressive therapy or death. The reality is that Dr. Thisted does not know whether this is the case, but is

[223] *See also* Section VIII.A, below.

simply making an assumption, without supporting data. Dr. Thisted's views also contradict how UTC interpreted the same data, as discussed in the next paragraph.

182. [redacted]

3. Agarwal 2015

183. In the case of Agarwal 2015, Dr. Thisted's criticisms of Dr. Channick again center around the fact that Agarwal reports results in a retrospective, single-arm study, which result in his opinion that those results cannot be used to draw any inferences whatsoever about efficacy, and are not equivalent to "demonstrating" efficacy. (Thisted Rpt., ¶¶ 236-243.) As I have explained above, I disagree that a POSA would completely discount the results reported in Agarwal, and I believe that Dr. Thisted is applying the wrong legal standard for reasonable expectation of success by requiring that the reference "demonstrate" efficacy.[225] Notably. Dr. Thisted does not deny or question the express disclosures of Agarwal 2015, which is that a statistically significant improved in 6MWD scores was reported in Group 3 PH patients.

184. I find it notable that Dr. Thisted, who is not a POSA, disagrees with the stated conclusions of the authors of Agarwal 2016 themselves (which include Dr. Waxman). (Thisted Rpt., ¶ 237.) Again, Dr. Thisted is focused on his criticism that Agarwal 2015 is a single-arm chart review, and his belief that he "cannot evaluate" if the conclusions of its authors were "justified." (Thisted Rpt., ¶ 239.) But Dr. Thisted's views on this subject do not supplant the expressly stated conclusions of the authors themselves, which were reported in the literature and would have been

[224] *See* Channick Opening Report at ¶ 259; *see also* Smith Depo Tr. at 78:24-789:10.
[225] *See also* Section VIII.A, below.

known to a POSA in 2020.

185. Dr. Thisted also again assumes, without evidence, that the fact of some patients discontinuing therapy suggests that the results reported in Agarwal are "too optimistic." (Thisted Rpt., ¶ 239.) The authors of Agarwal 2015, including Dr. Waxman, are undoubtedly experts and POSAs in this field, and the fact of some patient discontinuation would have been known to them and presumably incorporated into their analysis of the data. Yet this fact did not prevent them from expressly reporting that "Group 3 PH can be effectively and safely treated with iTre."

186. Similarly, Dr. Thisted assumes based only on the sample size that the patients studied in Agarwal 2015 were "not representative" of PH-ILD patients. (Thisted Rpt., ¶ 240.) As I have noted, Dr. Thisted is not a POSA and he does not provide any evidence to support his assumption that the sample cohort of 21 Group 3 PH patients studied in Agarwal 2015 are "not representative" of PH-ILD.

187. I also note that Dr. Thisted refers to information from a confidential internal UTC document that would not have been available to a POSA, and is thus irrelevant to the issues. (Thisted Rpt., ¶ 242.)

188. The "conclusion" section of Agarwal 2015, reproduced below, provides a useful summary of the state of the art that supports my response to Dr. Thisted's analysis. Dr. Thisted seems to ignore that the authors of this reference, which included Dr. Waxman, stated expressly that "Group 3-PH can be effectively and safely treated with iTre."[226]

[226] Agarwal 2015 at LIQ_PH-ILD_00148508.

Conclusion

Group-3 PH can be effectively and safely treated with iTre. Inhaled Treprostinil may offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling. A prospective clinical trial is indicated.

The fact that the authors also concluded that a prospective clinical trial is indicated does not undermine that Agarwal 2015 supports a reasonable expectation of success, as Dr. Thisted believes. Instead, this statement would be understood by a POSA in the context of the overall clinical drug development process, in which regulatory approval and labeling almost always requires the use of a prospective, randomized clinical trial. Thus, it makes sense that Dr. Waxman and his co-author would suggest this process, because this would be considered a necessary step towards Dr. Waxman's ultimate goal of label expansion for inhaled treprostinil from Group 1 patients to other groups such as Group 3. But this does not mean, as Dr. Thisted contends, that a POSA would not have had a reasonable expectation of success until after the indicated prospective clinical trial was completed. That this is true is shown by the words of Dr. Waxman and his co-author themselves, who again stated that "Group 3-PH can be effectively and safely treated with iTre."

189. Indeed, I find it notable that Dr. Thisted, who is not a POSA, disagrees with the stated conclusions of the authors of Agarwal 2016 themselves (which include Dr. Waxman). (Thisted Rpt., ¶ 237.) Again, Dr. Thisted is focused on his criticism that Agarwal 2015 is a single-arm chart review, but his views on this subject do not supplant the expressly stated conclusions of the authors themselves, which were reported in the literature and would have been known to a POSA in 2020.

4. Faria-Urbina 2018

190. Dr. Thisted criticizes Dr. Channick's discussion of Faria-Urbina 2018 in ¶¶ 244-

259 of his report. As he did with the other prior art references discussed above, Dr. Thisted centers his critique on the fact that Faria-Urbina 2018 was a single arm study, which "cannot be used to draw inferences about [] effectiveness." (Thisted Rpt., ¶ 244.) As I have explained throughout this report, I disagree that a POSA would not draw any inferences whatsoever from the statistically-significant data reported in Faria-Urbina 2018. Instead, as I noted above, the factual record is that clinicians like Dr. Waxman, who are POSAs, did draw inferences from these data, and they did conclude from it that there a reasonable basis to believe that inhaled treprostinil would be an effective to improve exercise capacity in PH-ILD patients – so much so that UTC elected to undertake a large, costly Phase III trial study without first seeking to confirm an efficacy signal in a smaller Phase II trial. (*See* Sections V.E and V.F.) Dr. Thisted also once again applies the wrong legal standard for reasonable expectation of success when he complains that the results of Faria-Urbina 2018 do not "demonstrate" efficacy.[227] (Thisted Rpt., ¶¶ 244-245.)

191. Dr. Thisted also assumes, without evidence, that the Faria-Urbina 2018 study suffered from "severe selection biases." (Thisted Rpt., ¶ 245.) The authors of Faria-Urbina 2018 are experts in the field and POSAs, unlike Dr. Thisted, who presumably are aware of the risk of selection bias, and who presumably accounted for it when they nevertheless relied on the results as justification to both treat patients off-label and go directly to a Phase III trial. I also disagree that Dr. Channick "ignores" the characteristics of the study that Faria-Urbina 2018 reports on. (Thisted Rpt., ¶ 246.) Dr. Channick accurately reports on the content and results of the prior art reference and was undoubtedly aware of these characteristics when rendering his opinion.

192. Also, as he did with regard to Agarwal 2015, Dr. Thisted simply assumes without evidence that the sample size reported on in Faria-Urbina 2018 "strongly indicates" that the data

[227] *See also* Section VIII.A, below.

is "not representative" of PH-ILD patients. I do not know of any reason, and Dr. Thisted does not supply any, why the data in Faria-Urbina 2018 is unrepresentative of PH-ILD patients, especially since at least 6 of the patients included in the results were PH-ILD patients

193. Dr. Thisted also assumes the results of Faria-Urbina 2018 are somehow tainted because, he says, the decision whether to perform the 6MWD test was based on "physicians' judgments." (Thisted Rpt., ¶ 248.) What Faria-Urbina 2018 discloses is that overall follow-up analysis was "performed at the discretion of the attending physician," and that this follow-up was based on a long list of functional assessments such as WHO functional class, in addition to other tests such as 6MWD test.[228] This does not support Dr. Thisted's assumption that the physicians involved only chose patients for performance of the 6MWD test when the physician believed they would perform well, or Dr. Thisted's unsupported assumption that a patients in the study were not tested for 6MWD if the physician judged that they "lacked the exercise capacity to successfully complete the test." The authors of Faria-Urbina 2018 are undoubtedly experts in their clinical field, and POSAs, unlike Dr. Thisted, and thus would presumably be aware of this risk of bias. Indeed, they expressly noted the limitations of the study,[229] but again this would not cause a POSA to entirely discount the results of the study (including statistically-significant 6MWD) – as indeed the factual record shows the results of Faria-Urbina 2018 were relied on by POSAs for further clinical development of inhaled treprostinil.

194. In his discussion of Dr. Waxman's public commentary on the results of Faria-Urbina 2018, Dr. Thisted appears to imply that Dr. Waxman intentionally biased the results of Faria-Urbina 2018 because it supported "his hypothesis." (Thisted Rpt., ¶¶ 249, 251.)

[228] Faria-Urbina 2018 at UTC_PH-ILD_009937.
[229] Faria-Urbina 2018 at UTC_PH-ILD_009941.

Importantly, Dr. Thisted identified no evidence at all to support his implied allegation that Dr. Waxman intentionally biased the results reported in Faria-Urbina 2018 because he believed the drug would likely work, indeed I do not see any basis for Dr. Thisted to attack Dr. Waxman's clinical judgment or scientific integrity in this way. Put another way, under Dr. Thisted's apparent view of the world, all study reports without placebo controls should be discounted entirely because the scientists pursuing the study must have been biased based on their optimism that the treatment would be effective. I disagree that such a level of intense skepticism is justified, or consistent with how a POSA would view the prior art, especially in this case where UTC's own actions in response to learning of the data in Agarwal 2015 and Faria-Urbina 2018 was to rely on it for significant further investments in an inhaled treprostinil clinical trial.

195. Dr. Thisted also notes that the authors conceded that their study design including the presence of pulmonary vascular disease might have influenced the results favoring the potential use of inhaled treprostinil in Group 3 PH. (Thisted Rpt., ¶ 249.) Dr. Thisted does not provide any medical or scientific rationale for why this statement could undermine a POSA's reasonable expectation of success, and I am not aware of any. Dr. Thisted also fails to acknowledge the next sentence in Faria-Urbina 2018, which notes that "Group 3 PH with impaired circulatory reserve is of major clinical interest in regard to PH-specific treatment,"[230] indicating that the patient population under study in Faria-Urbina 2018 would have been considered relevant by a POSA.

196. Dr. Thisted next focuses on his determination that at least 27 patients were excluded from analysis for various reasons. (Thisted Rpt., ¶ 250.) From this, Dr. Thisted, who is not a clinician or a POSA, simply assumes that those 27 patients "would be expected to have worse functional outcomes," Dr. Thisted does not point to any evidence, or rely on any other UTC expert

[230] Faria-Urbina 2018 at UTC_PH-ILD_009941.

in support of this assumption. Nor does he provide any evidence that this assumption would have led to an "optimistic bias" in the results reported in Faria-Urbina 2018.

197. Dr. Thisted notes that the authors of Faria-Urbina 2018 concluded that larger prospective studies were warranted and argues that this supports his opinion on reasonable expectation of success. (Thisted Rpt., ¶ 252.) But again, this applies the wrong legal standard, by assuming that a POSA cannot have a reasonable expectation of success unless there is sufficient randomized clinical data to allow them to draw a "conclusion" that the treatment is effective.

198. In response to Dr. Thisted's criticisms that Faria-Urbina 2018 includes a cohort of Group 3 patients, (Thisted Rpt., ¶ 253), as I noted above, PH caused by CPFE ("PH-CPFE") would be considered PH-ILD. I also note that the INCREASE trial included CPFE patients,[231] and the inhaled treprostinil clinical data reported in the '327 Patent included PH-CPFE patients.[232]

199. In ¶¶ 254-255 of his report, Dr. Thisted discusses transcripts of presentations by Dr. Waxman. Dr. Thisted provides his own interpretation of Dr. Waxman's statements, contending that at most they support larger clinical trials and thus "cannot be relied on to make an assessment of efficacy." Dr. Thisted's treatment of this evidence is flawed for two reasons. First, Dr. Thisted applies the wrong standard for reasonable expectation of success by arguing that it can only exist when large clinical trials have already provided a guarantee of success. Second, Dr. Thisted simply discounts the actual facts of how inhaled treprostinil was developed for PH-ILD, or the influence that the data in Faria-Urbina 2018 and Dr. Waxman's statements had on UTC, which I discussed above in Sections V.E and V.F. Dr. Waxman attempts to sidestep this evidence by contending that this evidence was supposedly "not immediately persuasive" to UTC, but he

[231] *See* NEJM Publication at UTC_PH-ILD_010795 (Table 1) (showing 42 of 163 patients (25.8%) in the inhaled treprostinil group had CPFE listed as "cause of lung disease.").
[232] *See, e.g.,* '327 Patent, Column 29 (Table 4) (showing equivalent information).

gives no evidence to support this assumption about how UTC reacted to this data. [redacted]

Dr. Thisted ignores this testimony because it runs counter to his narrative, but it establishes that UTC did "immediately" find this evidence persuasive. Further, UTC would have understood that a large clinical trial would be necessary to obtain regulatory approval for label expansion beyond Group 1 PH patients, but reasonable expectation of success is not judged by the same standard that the FDA uses when deciding whether to approve a label expansion.[235]

VII. RESPONSE TO DR. THISTEAD'S OPINION THAT THE ASSERTED CLAIMS OF THE '327 PATENT ARE NOT ANTICIPATED BY FARIA-URBINA 2018

A. Independent Claim 1

200. Dr. Thisted's anticipation opinions in ¶¶ 267-284 of his report boil down to his assertion that the Faria-Urbina 2018 report does not disclose a method of improving exercise capacity in a PH-ILD patient by administration of treprostinil, all because Faria-Urbina 2018 is a single-arm retrospective chart review. Importantly, Dr. Thisted reaches this opinion only by ignoring the literal disclosures of the reference, which expressly reports that the patients in the study, including PH-ILD patients, did experience a significant improvement in 6MWD. For example, Dr. Thisted essentially ignores the literal disclosures of the Faria-Urbina 2018 reference

[233] Channick Opening Report at ¶ 218; *see also* Waxman Depo. Tr. at 127:11-24 [redacted].

[234] Channick Opening Report at ¶ 37; *see also* Smith Depo. Tr. at 48:5-17, 49:8-16; 2015 Waxman Presentation (UTC_PH-ILD_082484), Waxman Depo. Tr. at 127:11-24 ([redacted], 131:19-132:5 ([redacted]).

[235] *See also* Section VIII.A, below.

which state that Group 3 PH patients (including PH-ILD patients) experienced a ""significant improvement in . . . 6-min walk distance."[236] The reference also expressly discloses that "patients with Group 3 PH treated with [inhaled treprostinil,] . . . therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance."[237] These disclosures are also discussed by Dr. Channick. (*See* Channick Opening Report, ¶¶ 128-130.)

201. Dr. Thisted's response to these express and unambiguous disclosures is to essentially ignore them, on the basis of his claim that a POSA would "doubt" the veracity of the claims made by the authors because they were based on a single-arm retrospective study, pointing to supposed concerns such as selection bias or the presence of concomitant medications. There are several problems with this.

202. First, Dr. Thisted appears to be applying an incorrect legal standard for anticipation, which asks whether a prior art reference discloses, expressly or inherently, the subject matter of the claim. As shown by the quoted language above, and as further detailed by Dr. Channick, the Faria-Urbina 2018 reference clearly meets this standard. Instead, Dr. Thisted seems to be supplanting his own interpretation of the law of anticipation, in which the express disclosures of a reference are irrelevant if a POSA would have reason to doubt the reliability of the statements at issue. As I have discussed above in the context of my response to Dr. Thisted's criticisms of Dr. Channick (Section VI.B.4), I do not agree that a POSA would doubt the veracity of the express statements made by the authors of Faria-Urbina 2018.

203. Second, Dr. Thisted's refusal to acknowledge the written words on the page of Faria-Urbina 2018 is also contradicted by the statements of other, skilled clinicians who actually

[236] Faria-Urbina 2018 at UTC_PH-ILD_009936.
[237] *Id.* at UTC_PH-ILD_009939.

studied treprostinil in PH-ILD patients at the time, such as Dr. Waxman. For example, Dr. Waxman, the senior author of Faria-Urbina 2018, testified that the reference disclosed that "patients in Group-3 treated with inhaled treprostinil … had significantly improved WHO functional class and six-minute walk test distance results."[238] Furthermore, Dr. Waxman acknowledged during the Waxman 2017 Presentation that the data in Faria-Urbina 2018 was "additional support" that inhaled treprostinil could treat PH patients with "advanced lung disease":

> And so to finish up, hopefully, you'll agree that at least these pilot findings do provide some support -- additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And that these findings also provide additional evidence supporting more at – larger clinical trials in patients with this form of pulmonary vascular disease.[239]

Dr. Faria-Urbina, the lead author of Faria-Urbina 2018, also confirmed that the reference disclosed statistically significant improvements in 6MWD, WHO-FC, resting peripheral oxygen saturation from using inhaled Treprostinil:

> Q. And based on your retrospective with the 6-minute walk test, the patients actually improved on the 6-minute walk test, correct?
>
> A. That's not what the conclusion is saying.
>
> Q. In the results section.
>
> A. Let me read the results. It says that -- yes, "we observed a significant improvement in functional class and 6-minute walk test" -- "distance."
>
> Q. And there's a p-value identified there, "p=0.0222." Do you see that?
>
> A. Yes.
>
> Q. What does that mean?

[238] *See* Waxman Depo Tr. at 102:17-23.
[239] 2017 Waxman Tr. at 17:8-16; Waxman Depo. Tr. at 91:7-13.

A. That means the statistical significance.

Q. And so there was a statistical significance observed with the 6-minute walk test?

A. Yes.

Q. Was there a statistical significance observed with respect to functional class?

A. Yes.

Q. There's a sentence in the results, it says, "without a deleterious effect on resulting peripheral oxygen saturation." Do you see that?

A. Yes.

[…]

Q. And was there a statistical significant result observed with respect to resting peripheral oxygen saturation?

A. Yes.[240]

Dr. Thisted's supposed concerns with the quality of the data in the reference, which I addressed above, do not have any bearing on whether the reference reports (as it does) the claimed improvement in exercise capacity in Group 3 PH patients treated with inhaled treprostinil.

204. For these reasons, I disagree with Dr. Thisted's opinion that Faria-Urbina 2018 does not anticipate Claim 1 of the '327 patent. And because Faria-Urbina 2018 does anticipate Claim 1 of the '327 patent, I also disagree with Dr. Thisted's opinion that Faria-Urbina 2018 does not anticipate dependent Claims 2–11 and 14–19 depend from Claim 1 of the '327 patent.[241] And as explained in the sections below, I further disagree with Dr. Thisted's specific opinions that dependent claims 2-3, 6, and 17-19 are not anticipated by Faria-Urbina 2018.

[240] Faria-Urbina Tr. at 98:14 – 100:24.
[241] Thisted Rebuttal Report at ¶ 275.

B. Dependent Claims 2-3 and 17-19

205. I disagree with Dr. Thisted's opinion that dependent claims 2-3 and 17-19 are not anticipated by Faria-Urbina 2018.[242] For context, I have reproduced these dependent claims below:

	'327 Patent Claims
Claim 2	
2	The method of claim **1**, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
Claim 3	
3	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
Claim 17	
17	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.
Claim 18	
18	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.
Claim 19	
19	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

I understand Dr. Thisted has taken the position that dependent claims 2-3 and 17-19 "require that the administering cause that increase" of 6MWD.[243] However, Dr. Thisted's analysis in ¶¶ 278-282 is flawed.

[242] *See, e.g.,* Thisted Rebuttal Report at ¶¶ 275-283.
[243] Thisted Rebuttal Report at ¶ 278.

1. Response to Dr. Thisted's Opinions in ¶ 279 that Faria-Urbina 2018 Failed To Demonstrate Any Inhaled Treprostinil Treatment Effect On 6MWD Because Of Statistical Biases

206. Despite admitting that the improvement in patient 6MWD "achieved statistical significance," Dr. Thisted opines in ¶ 279 that Faria-Urbina 2018 failed to demonstrate any inhaled treprostinil treatment effect on 6MWD because of statistical biases.

207. First, Dr. Thisted speculates that the statistically significant improvement could be attributed to other factors such as favorable "patient selection, […] placebo effects, physician or patient selection, natural disease course, and systematic selection of which treprostinil patients to analyze and which to discard." Dr. Thisted fails to account for how PH-ILD is a chronic and progressive disease, that is expected to worsen over time, thus highlighting the clinical importance of a statistically-significant positive treatment effect.[244] I further note that Dr. Thisted identifies no evidence that a PH-ILD patient's exercise capacity can spontaneously improve, and therefore has no basis to opine that natural disease course confounds the data reported in Faria-Urbina 2018. Furthermore, Dr. Thisted does not provide any evidence that selection biases affected the data reported in Faria-Urbina 2018, and I note that 6MWD was not reported to be part of patient inclusion criteria of Faria-Urbina 2018.

208. Second, Dr. Thisted incorrectly speculates that sildenafil and tadalafil could have caused the 6MWD improvement in the four patients that received treprostinil in conjunction with sildenafil and tadalafil. Dr. Thisted identifies no evidence to support the speculation that the treatment effect observed in Faria-Urbina 2018 was caused by dual therapy as opposed to by inhaled treprostinil (as the authors of the study concluded). Dr. Thisted also fails to account for

[244] *See, e.g.,* Sections V.A. and V.C above (discussing PH as a progressive disease); *see also* Channick Opening Report ¶ 18; Hill Opening Report ¶¶ 52-57; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 162:1 – 163:2.

how the data shown in Figure 3 shows that seven other Group 3 PH patients saw an increase in 6MWD even though they didn't receive sildenafil and tadalafil:[245]

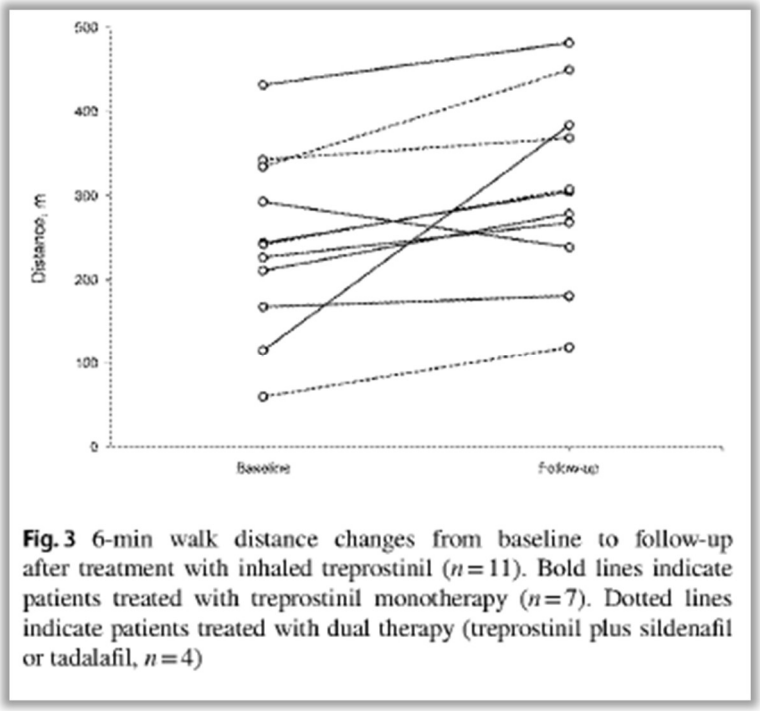

Fig. 3 6-min walk distance changes from baseline to follow-up after treatment with inhaled treprostinil ($n=11$). Bold lines indicate patients treated with treprostinil monotherapy ($n=7$). Dotted lines indicate patients treated with dual therapy (treprostinil plus sildenafil or tadalafil, $n=4$)

This same data does not indicate any reason to think that the presence of dual therapy impacted the effect of inhaled treprostinil on the patients 6MWD, as I noted above the authors of the study did not indicate any concern that the presence of dual therapy might be confounding their results. Finally, I note that the exclusion criteria reported in Faria-Urbina 2018 state that patients who has "treatment with another PH-specific drug added in a period < 3 months" were excluded from the analysis.[246]

209. Lastly, Dr. Thisted fails to address how the authors of Faria-Urbina 2018 stated that their subanalysis of treated PH-COPD, PH-ILD, and PH-CPFE patients "demonstrated that the tendency for improved functional class and 6-min walk distance, without significant deleterious

[245] Faria-Urbina 2018 at UTC_PH-ILD_009940 (Fig. 3).
[246] Faria-Urbina 2018 at UTC_PH-ILD_009937; *see also* Waxman Depo Tr. at 96:19 – 97:6.

effect on SpO2 that was observed in the entire study population was maintained in each subcohort."[247] As these authors were all qualified enough to be considered POSAs, it is my opinion that a POSA would understand that the observed changes in 6MWD are provided by administering inhaled treprostinil as recited in claims 2-3 and 17-19.

210. Therefore, I disagree with Dr. Thisted's opinion in ¶ 279 that Faria-Urbina 2018 failed to demonstrate any inhaled treprostinil treatment effect on 6MWD because of supposed statistical biases.

2. Response to Dr. Thisted's Opinions in ¶ 280 that the Statistical Comparison of Selected Patients in Faria-Urbina 2018 Cannot Establish That Improvements Were a Consequence of Inhaled Treprostinil

211. Dr. Thisted incorrectly opines in ¶ 280 that the 6MWD improvements of "highly selected patients" in Faria-Urbina 2018 "cannot establish that those changes were a consequence of their common treatment or that those changes were different from what comparably selected patients not treated with treprostinil would incur."[248]

212. Once again, Dr. Thisted's opinion is based on the mistaken belief that a patent claim can only be anticipated by blinded studies. But Dr. Thisted ignores that the authors of the Faria-Urbina 2018 reference literally states that Group 3 PH patients (including PH-ILD patients) experienced a "significant improvement in . . . 6-min walk distance."[249] The reference also expressly discloses that "patients with Group 3 PH treated with [inhaled treprostinil,] . . . therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance."[250] Even Dr. Thisted acknowledges that the 6MWD data in Faria-Urbina 2018 shows that patients receiving

[247] Faria-Urbina 2018 at UTC_PH-ILD_009941 (Citing Tables S2-S4).
[248] Thisted Rebuttal Report at ¶ 280.
[249] Faria-Urbina 2018 at UTC_PH-ILD_009936.
[250] *Id.* at UTC_PH-ILD_009939.

inhaled treprostinil "likely had real changes."[251] Nevertheless, Dr. Thisted contradicts himself and ignores the express disclosures of Faria-Urbina 2018 on the basis that the unblinded study design of Faria-Urbina 2018 does not teach "whether inhaled treprostinil provides increases in 6MWD as compared to patients not receiving inhaled treprostinil." As Faria-Urbina 2018 discloses data reflecting the recited improvement in 6MWD following the administering of inhaled treprostinil, I agree with Dr. Channick that Faria-Urbina 2018 anticipates the dependent claims 2-3 and 17-19.

213. Furthermore, Dr. Thisted is incorrect that the Faria-Urbina 2018 data "cannot establish that those changes were a consequence of their common treatment" because Dr. Thisted fails to account for how PH-ILD is a chronic and progressive disease, that is expected to worsen over time, thus highlighting the clinical importance of a statistically-significant positive treatment effect.[252] I further note that Dr. Thisted identifies no evidence that a PH-ILD patient's exercise capacity can spontaneously improve, and therefore has no basis to opine that natural disease course confounds the data reported in Faria-Urbina 2018.

214. Therefore, in view of these considerations and Dr. Thisted's own admission that the data in Faria-Urbina 2018 shows that patients receiving inhaled treprostinil "likely had real changes," it is my opinion that Faria-Urbina 2018 anticipates dependent claims 2-3 and 17-19.

3. Response to Dr. Thisted's Opinions in ¶ 281 that Faria-Urbina 2018 Does Not Report 6MWD Improvements After the Recited Time Periods

215. Dr. Thisted incorrectly opines in ¶ 281 that the Faria-Urbina 2018 fails to report changes in 6MWD after the recited time periods in dependent claims 3 and 17-19 because "all follow-up assessments of 6MWD were done only in patients with ≥ 3 months (13 weeks) follow-

[251] Thisted Rebuttal Report at ¶ 280.
[252] *See, e.g.,* Sections V.A. and V.C above (discussing PH as a progressive disease); *see also* Channick Opening Report at ¶ 18; Hill Opening Report at ¶¶ 52-57; Rajan Saggar Sept. 17, 2024 Depo. Tr. at 162:1 – 163:2.

up." For context, I have reproduced these dependent claims below:

Claim 3	
3	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
Claim 17	
17	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.
Claim 18	
18	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.
Claim 19	
19	The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

216. Dr. Thisted is incorrect that Faria-Urbina 2018 does not teach 6MWD improvements after 8 weeks, 12 weeks, or 16 weeks as recited by dependent claims 3 and 17-19 because Dr. Thisted misunderstands the plain language of the claims. I understand from Dr. Channick's opening report that claims 3 and 17-19 means that the recited increase in 6MWD (i.e., 10m or 15m) must be achieved during the period of time following the administering of treprostinil for the recited time period of 8 weeks, 12 weeks, or 16 weeks.[253] According to Table 2 from Faria-Urbina 2018 below, average patient 6MWD increased by 65m from an average baseline of 243m to an average of 308m after receiving inhaled treprostinil for 3 months or more:[254]

[253] Channick Opening Report at ¶¶ 140, 155-157.
[254] Channick Opening Report at ¶¶ 140, 155-157; Faria-Urbina 2018 at UTC_PH-ILD_009940 (Table 2) (showing 6MWD average).

Table 2 Changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil

	N	Baseline	Follow-up	*p* value
Clinical assessment	22			
WHO functional class I/II/III/IV (n)		0/4/15/3	2/7/12/1	0.041
SpO_2 at rest (%)		92 ± 6	94 ± 4	0.014
Pulmonary function test	16			
FEV_1 (% predicted)		65 ± 27	60 ± 25	0.23
FVC (% predicted)		67 ± 26	59 ± 22	0.12
FEV_1/FVC (% predicted)		96 ± 15	96 ± 18	0.99
Echocardiography	13			
TRV (m/s)		3.7 ± 0.5	3.6 ± 0.5	0.66
Estimated sPAP (mmHg)		62 ± 18	60 ± 22	0.68
6-min walk test	11			
Distance (m)		243 ± 106	308 ± 109	0.022
Final dyspnea Borg score		6 ± 2	4 ± 2	0.15
Final SpO_2 (%)		82 ± 8	76 ± 9	0.12
3-min step test with metabolic cart	13			
VE/VCO_2 slope		45.9 ± 19.7	47.8 ± 20.1	0.55
Δ $P_{ET}CO_2$ (mmHg)		0.0 ± 1.9	-0.9 ± 2.6	0.081
Final SpO_2 (%)		81 ± 8	80 ± 7	0.76

Data are presented as *n* or mean ± SD

WHO World Health Organization, SpO_2 arterial oxygen saturation measured by pulse oximetry, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *TRV* tricuspid regurgitant jet velocity, *sPAP* systolic pulmonary arterial pressure, *VE* minute ventilation, VCO_2 carbon dioxide production, Δ change in, $P_{ET}CO_2$ end-tidal carbon dioxide tension

Based on the plain meaning of the dependent claims, I agree with Dr. Channick's opinion that Faria-Urbina 2018 anticipates dependent claims 3 and 17-19 because the data reports a greater increase in 6MWD (65m) than required by the claims. Moreover, the fact that the follow-up period may have varied from patient-to-patient does not change the fact that the recited improvements were achieved (or exceeded) following the administration of inhaled treprostinil.

217. Therefore, I disagree with Dr. Thisted's opinion in ¶ 281 that Faria-Urbina 2018 failed to report the required increases in 6MWD.

4. Response to Dr. Thisted's Opinion That Dependent Claim 6 is Not Anticipated by Faria-Urbina 2018

218. I further disagree with Dr. Thisted's opinion that dependent claim 6 is not anticipated by Faria-Urbina 2018.[255] For context, I have reproduced this dependent claim below:

[255] *See* Thisted Rebuttal Report at ¶ 284.

	'327 Patent Claims
Claim 6	
6	The method of claim **1**, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.

Dr. Thisted has taken the position that Faria-Urbina 2018 does not anticipate dependent claim 6 because it "teaches nothing about reduction of at least one exacerbations and provides no information whatever about 'reduction of at least one exacerbations of the interstitial lung disease.'"[256] I disagree because Dr. Thisted's opinion is not tethered to what a POSA would consider to be a measurement of an exacerbation.

219. As explained by Dr. Channick,[257] the '327 patent defines an exacerbation of ILD as "an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality."[258] Dr. Channick further explains that he and other POSAs, like Dr. Waxman, would understand these exacerbations to comprise of worsening oxygenation and shortness of breath, which are both signs of respiratory deterioration.[259] In this regard, POSAs would understand that the 6MWD, dyspnea (i.e., shortness of breath), and WHO-FC assessments in Table 2 from Faria-Urbina 2018 are equivalent to assessing exacerbations of ILD.[260] Table 2 of Faria-Urbina 2018 presents this data as follows:

[256] Thisted Rebuttal Report at ¶ 284.
[257] Channick Opening Report at ¶¶ 141-146.
[258] '327 patent at 22:12-15.
[259] Waxman Depo. Tr. at 115:21-116:2 (Dr. Waxman testifying that clinical exacerbations include worsening oxygenation and worsening shortness of breath and that these metrics reflected improvements in WHO-FC and 6MWD)).
[260] Channick Opening Report at ¶¶ 141-145.

Table 2 Changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil

	N	Baseline	Follow-up	*p* value
Clinical assessment	22			
WHO functional class I/II/III/IV (n)		0/4/15/3	2/7/12/1	0.041
SpO_2 at rest (%)		92 ± 6	94 ± 4	0.014
Pulmonary function test	16			
FEV_1 (% predicted)		65 ± 27	60 ± 25	0.23
FVC (% predicted)		67 ± 26	59 ± 22	0.12
FEV_1/FVC (% predicted)		96 ± 15	96 ± 18	0.99
Echocardiography	13			
TRV (m/s)		3.7 ± 0.5	3.6 ± 0.5	0.66
Estimated sPAP (mmHg)		62 ± 18	60 ± 22	0.68
6-min walk test	11			
Distance (m)		243 ± 106	308 ± 109	0.022
Final dyspnea Borg score		6 ± 2	4 ± 2	0.15
Final SpO_2 (%)		82 ± 8	76 ± 9	0.12
3-min step test with metabolic cart	13			
VE/VCO_2 slope		45.9 ± 19.7	47.8 ± 20.1	0.55
Δ $P_{ET}CO_2$ (mmHg)		0.0 ± 1.9	-0.9 ± 2.6	0.081
Final SpO_2 (%)		81 ± 8	80 ± 7	0.76

Data are presented as *n* or mean ± SD

WHO World Health Organization, SpO_2 arterial oxygen saturation measured by pulse oximetry, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *TRV* tricuspid regurgitant jet velocity, *sPAP* systolic pulmonary arterial pressure, *VE* minute ventilation, VCO_2 carbon dioxide production, Δ change in, $P_{ET}CO_2$ end-tidal carbon dioxide tension

220. I understand from Dr. Channick that improvements in 6MWD reflect a reduction in exacerbations of ILD because it represents a reduction in respiratory deterioration.[261] Because Faria-Urbina 2018 discloses a statistically significant improvement of 6MWD (n = 11, p value= 0.022), Faria-Urbina 2018 discloses a statistically significant reduction in exacerbations.

221. I understand from Dr. Channick that a decrease in dyspnea (shortness of breath) reflects a reduction in exacerbations of ILD because shortness of breath and worsening oxygenation are signs of respiratory deterioration.[262] I further understand from Dr. Channick that Dr. Waxman testified that a decrease in dyspnea is reflected in improvements in WHO functional class and 6MWD.[263] In relevant part, Dr. Waxman testified:

[261] Channick Opening Report at ¶ 144.
[262] Channick Opening Report at ¶ 145.
[263] Channick Opening Report at ¶ 145; *see also id. at* ¶ 25. (citing Waxman Depo. Tr. at 116:3-18. (testifying that a decrease in shortness of breath (dyspnea) was reflected in the "WHO functional class and [] six-minute walk distance").

Q. Did you see a decrease in shortness of breath?

A. Yes.

Q. Was that reflected in the WHO FC measurements?

A. I would say both the WHO functional class and the six-minute walk distance.[264]

Here, Faria-Urbina 2018 discloses statistically significant improvements in WHO-FC and 6MWD. Based on my understanding of Dr. Channick's report and Dr. Waxman's testimony, these improvements correspond to a statistically significant reduction of dyspnea, which is an exacerbation of ILD.

222. I understand from Dr. Channick that improvements in WHO-FC assessment reflect a reduction in reflect a reduction in exacerbations because WHO-FC measures the severity of a patient's pulmonary hypertension symptoms.[265] Because Faria-Urbina 2018 discloses a statistically significant improvement of in functional class (n = 22, functional class III-IV 82 vs. 59%, p = 0.041), Faria-Urbina 2018 discloses a statistically significant reduction in exacerbations.

223. Therefore, I disagree with Dr. Thisted's opinion in ¶ 284 that Faria-Urbina 2018 failed to report any reductions in exacerbations of ILD.

VIII. RESPONSE TO DR. THISTED'S OPINION THAT THE ASSERTED CLAIMS OF THE '327 PATENT ARE NOT OBVIOUS

A. Dr. Thisted Applies the Wrong Standard for Reasonable Expectation of Success.

224. One primary issue with Dr. Thisted's opinion is that it relies on an improper standard for reasonable expectation of success as noted above. This standard contradicts the opinions of other UTC experts, and is largely detached from the realities of the drug development

[264] Waxman Depo. Tr. at 116:12-18.
[265] Channick Opening Report at ¶ 143.

process and the perspective of a POSA in this field.

225. As discussed above in Section V-C of my report, clinical testing is a phased process that seeks to obtain increasing evidence to confirm that a drug is safe and effective for the purposes of FDA approval. Each phase is intended to build on the results of previous testing and demonstrate that it is worth the cost of progressing to the next phase of clinical testing. In this respect, clinical testing seeks to progressively develop knowledge regarding a drug's safety and efficacy.

226. This is particularly evident in the transition between Phase II and Phase III clinical trials, which are both designed to measure drug efficacy (in addition to drug safety). Phase II clinical trials typically involve single-arm or randomized testing with a small group of a few hundred patients and are designed to provide an early signal that a drug may effectively treat a specific disease. Phase III clinical trials typically involve multi-center, randomized, and blinded testing with hundreds of patients, providing additional and more robust confirmation of drug efficacy and safety. However, this does not imply that drug efficacy can only be determined after Phase III trials. In fact, it would be highly unlikely for drug manufacturers to invest in costly Phase III trials without the prior evidence of efficacy obtained from Phase II trials, whether through single-arm or randomized testing. These earlier trials must already provide compelling evidence of the drug's potential, justifying the transition to the more expensive Phase III stage. Therefore, the multi-center, randomized, and blinded design of Phase III trials should be viewed as a confirmation of the drug's efficacy, building on the expectations derived from the smaller-scale, Phase II studies.

227. Dr. Thisted's report takes a position on how a POSA interacts with statistically significant clinical data that contradicts these well-established principles of drug development and

clinical testing. Dr. Thisted's opinion is essentially that a POSA cannot reasonably expect a drug to successfully treat a disease until that drug has demonstrated efficacy in the kind of multi-center, randomized, and blinded testing associated with Phase III clinical trials. This standard is inconsistent with the realities of drug development. Reasonable expectation of drug efficacy can result from other sources, such as small-scale studies, and does not absolutely require the completion of multi-center, randomized, and blinded testing of large patient populations. Such testing is clearly important to our system of ensuring only safe and effective drugs are approved, but these studies are more properly seen as providing additional and confirmatory evidence of drug efficacy already indicated small-scale, single-arm studies. A POSA does not consider such randomized clinical trials to be the first-ever evidence of drug efficacy as Dr. Thisted contends.

228. Moreover, I note that Dr. Thisted's opinions are particularly inapplicable to the factual history of treprostinil use as of 2020, and the events which lead to the INCREASE trial and the '327 patent. As detailed above in Sections V.D, V.E, and V.F, it was precisely the same prior art studies that Dr. Thisted criticizes that led UTC to jump directly to a full Phase III trial of inhaled treprostinil in PH-ILD patients, based on the strength of this early data and widespread off-label use, thereby skipping a Phase II trial which would ordinarily be employed to ascertain an efficacy signal.

B. Dr. Thisted's Opinions Improperly Rely on Information that Would Not Have Been Available to a POSA.

229. An additional flaw in Dr. Thisted's opinions is his frequent reliance on information that would not have been known to or available to a POSA as of 2020, such as the contents of internal UTC documents, or the results of clinical trials which were not reported until after 2020.

230. For example, Dr. Thisted cites internal, confidential UTC documents that would not be available to a POSA as of 2020. [redacted]

[redacted] Accordingly, that information would not be available to a POSA and is irrelevant to the issue of obviousness. (*See also id.,* ¶¶ 164, 170-173, 176, 242, 306 (discussing nonpublic information relating to the Agarwal 2015 reference)

231. [redacted]

232. Dr. Thisted also relies heavily on information that did not exist as of 2020, and thus could not have been known by a POSA. In particular, Dr. Thisted repeatedly invokes the termination in Sept. 2022 of the PERFECT study in PH-COPD patients as providing evidence that use of inhaled treprostinil to improve exercise capacity in PH-ILD patients would not have been obvious *as of 2020*. (*See, e.g.,* Thisted Rpt., ¶¶ 206-209, 211, 215, 255, 264.) However, information from 2022 and later cannot inform the question of obviousness if a POSA could not have known about it as of 2020.

233. I note that Dr. Thisted's reliance on these materials appears to contradict his statement that he understands that "an obviousness analysis must be performed from the perspective of a POSA as of the effective filing date" and that "when considering evidence, [he] should not consider what is known today." (*See* Thisted Rpt., ¶¶, 49, 51.) Dr. Thisted's reliance on confidential internal UTC documents and post-priority date evidence such as the PERFECT trial, do not support Dr. Thisted's nonobviousness arguments, because those materials would not have been available to a POSA.

C. Response to Dr. Thisted's Opinion that Asserted Claims 9-10 of the '327 Patent Are Not Rendered Obvious by the February 2020 Press Release in Combination with Saggar 2014 Because the POSA Would Not Have a Reasonable Expectation of Success of Arriving at the Claimed Methods.

234. In this section, I respond to ¶¶ 286-288 of Dr. Thisted's report.

235. As noted above, I disagree with Dr. Thisted's opinion that Saggar 2014 fails to disclose an improvement in FVC simply because its results are not reported as being statistically significant.[266] And, in the context of obviousness, I agree with Dr. Channick's opinion that a POSA would have a reasonable expectation of success in achieving a statistically significant improvement in FVC by using inhaled treprostinil when the teachings of Saggar 2014 are combined with the Feb. 2020 Press Release. The correct legal standard for obviousness and reasonable expectation of success does not require perfect predictability or an assurance that success will be achieved.[267] Instead, Dr. Channick as a POSA opines that a POSA would have a reasonable expectation that a larger study would succeed in detecting improved FVC to a statistically significant degree, and I agree. I further disagree with Dr. Thisted's interpretation of Saggar 2014 in ¶ 287 that "Saggar 2014 expressly informs the POSA not to rely on the reported FVC data." (Emphasis added.) Saggar 2014 does not contain any such "express" statement, but only reports accurately that the improved FVC data it reports did not achieve statistical significance in that small study. I disagree that a POSA would interpret this simple statement as an instruction to discount all of the results of the study; on the contrary a POSA would recognize from Saggar 2014's express teachings that its study found that 10 out of 15 patients did experience improved predicted % FVC.[268]

[266] *See* Section VI.B.1, above.
[267] *See* Section VIII.A, above.
[268] *See* Section VI.B.1, above.

D. Response to Dr. Thisted's Opinion that Asserted Claims 1–11 and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Faria-Urbina 2018.

236. In this section, I respond to ¶¶ 289-297 of Dr. Thisted's report.

237. Dr. Thisted repeats his contention that an inhaled treprostinil treatment effect is "absent" from Faria-Urbina 2018 and "missing" from the prior art. (Thisted Rpt., ¶ 290.) As I explained above, this is incorrect. Faria-Urbina 2018 expressly discloses that inhaled treprostinil improved 6MWD scores to a statistically significant degree.[269] Because Dr. Thisted totally discounts any data from single-arm studies, Dr. Thisted's approach is to simply assume that the results disclosed in Faria-Urbina do not exist. As I have explained, a POSA would not completely discount all of the teachings of Faria-Urbina 2018 simply because it was a single-arm study.[270] I note also in this regard that claim 1 of the '327 does not require a statistically significant improvement in exercise capacity, nor does it require an improvement as shown through a large, randomized clinical trial of the type that would be used for FDA approval.

238. Similarly, when discussing claims 2-3, 7-8, and 17-19 in ¶¶ 294-297 of his report, Dr. Thisted again centers his opinion on the contention that the express disclosures of Faria-Urbina 2018 do not count because that reference is reporting on a single-arm study. As I have detailed above, this opinion does not erase from existence that Faria-Urbina 2018 expressly discloses that patients receiving inhaled treprostinil showed improved 6MWD scores to a statistically significant degree.[271] Dr. Thisted discusses the topics of causality and that the prior art fails to "demonstrate" that the treatment effects observed in Faria-Urbina 2018 were caused by inhaled treprostinil as opposed to some other cause. But these opinions apply the wrong legal standard, in two ways.

[269] *See* Section VI.B.4, above.
[270] *See* Section VI.B.4, above.
[271] *See* Section VI.B.4, above.

First, requiring that the prior art expressly demonstrate statistically significant treatment effects resulting from inhaled treprostinil uses the legal standard for anticipation, not obviousness. Secondly, the correct legal standard for obviousness requires only that a POSA would have had a reasonable expectation of success, based on the teachings of the prior art.[272]

239. As I have detailed above and reiterate here, I agree with Dr. Channick's opinion that the express disclosure of a statistically significant improvement in exercise capacity in Faria-Urbina 2018, especially when combined with all the other evidence available to a POSA, would have provided a POSA with that reasonable expectation of success.[273] In the context of claims 7 and 8 reciting a "reduction in clinical worsening events," I note that Dr. Channick opines that the prior art's express disclosure of increase in 6MWD, rather than a decrease, constitute a disclosure of a reduction in clinical worsening events,[274] and I agree.

E. Response to Dr. Thisted's Opinion that Asserted Claims 4-5, 6, and 9-10 of the '327 patent are not rendered obvious by Faria-Urbina 2018 in combination with the '793 patent and Saggar 2014

240. In this section, I respond to ¶¶ 298-301 of Dr. Thisted's report.

241. In ¶ 298, Dr. Thisted repeats his assertion that "Saggar 2014 does not disclose a parenteral treprostinil treatment effect." This is incorrect. Saggar 2014 discloses what it discloses, and as I explained above those disclosures include a statistically significant improvement in 6MWD.[275] I do not agree with Dr. Thisted's approach of simply discarding or ignoring the express teachings of the prior art, simply because of Saggar 2014 was a single-arm study and other features of that study.

242. Concerning claims 4 and 5, in ¶ 299 of his report Dr. Thisted opines that the prior

[272] *See* Section VIII.A, above
[273] *See* Section VI.B.4, above.
[274] *See* Channick Opening Report at ¶¶ 327-330.
[275] *See* Sections V.D.2 and VI.B.2, above.

art fails to disclose the claimed reduction in plasma NT-proBNP, ignoring that Saggar 2014 expressly discloses not only a reduction in BNP activity, but also that this reduction was statistically significant.[276] I understand from Dr. Channick that, based on his clinical experience, BNP and NT-proBNP are interchangeable.[277] Apart from this, Dr. Thisted opines that Saggar 2014 "does not teach a parenteral treprostinil treatment effect." As I discussed above, that is incorrect. This is also why I disagree with Dr. Thisted's opinion concerning claim 6 in ¶ 300 of his report, which is based on the incorrect statement that Saggar 2014 does not disclose a treatment effect. Dr. Thisted also states his opinion in ¶ 299 that there would not be a reasonable expectation of success, although he provides no explanation for this opinion and instead just cites back to his opinions criticizing single-arm trials, which I have responded to above.

243. Concerning claims 9 and 10, in ¶ 301 of his report, Dr. Thisted argues that Faria-Urbina 2018 "teaches away" from the invention recited in claims 9 and 10 because it reported a worsening of % predicted FVC after treatment with inhaled treprostinil. I find this opinion puzzling, since Table 2 of Faria-Urbina shows that the % predicted FVC results were not statistically significant.[278] It is notable to me that Dr. Thisted is so inconsistent in his analysis of the data – in this instance, where it supports UTC's cause, he is apparently happy to rely on data that lacks statistical significance. Yet when responding to Dr. Channick's opinions, Dr. Thisted considers lack of statistical significance to be a fatal flaw. These views cannot be reconciled and show that Dr. Thisted's analysis of the prior art is not consistent. In other respects, Dr. Thisted's opinions in this section simply rehash his earlier-stated opinions regarding reasonable expectation of success, which I have already responded to above.

[276] *See* Section V.D.2; Saggar 2014 at LIQ_PH-ILD_00000230 (Table 4).
[277] *See* Channick Opening Report at ¶ 312.
[278] Faria-Urbina 2018 at UTC_PH-ILD_009940 (Table 2).

F. Response to Dr. Thisted's Opinion that Asserted Claims 1–11 and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Agarwal 2015

244. In this section, I respond to ¶¶ 302-315 of Dr. Thisted's report.

245. Similar to his approach for the Saggar 2014 and Faria-Urbina 2018 references, in this part of his report Dr. Thisted asserts that "Agarwal 2015 fails to disclose an inhaled treprostinil effect." (Thisted Rpt., ¶ 302.) And as his treatment of the other prior art, Dr. Thisted is incorrect here as well. Agarwal discloses what it discloses, and there can be no dispute that it expressly discloses that patients treated with inhaled treprostinil had a statistically significant improvement in 6MWD score.[279] There also can be no dispute that Agarwal 2015 expressly discloses that "Group 3-PH can be effectively and safely treated with iTre."[280] Dr. Agarwal's refusal to accept the express teachings of this reference because it reports on a single-arm study is contrary to how a POSA would have (and did) understand and rely on these disclosures, as I explain above.[281]

246. In this section of his report Dr. Thisted repeats his other criticisms of Agarwal 2015, explaining his "doubt" about the results of the study and his speculation that the disclosed results are "too optimistic." (Thisted Rpt., ¶¶ 303-305.) I addressed these criticisms above,[282] and incorporate those responses here. Dr. Thisted also includes the criticism that "patients in whom the drug was ineffective were never measured for changes in 6MWD and were not included in the reported results." (Thisted Rpt., ¶ 307.) I do not see any basis for Dr. Thisted's opinion in this regard. It appears to be based on an unfounded assumption that inhaled treprostinil was not, and would not have been, effective in any of the patients who withdrew or were excluded from the follow up analysis in Agarwal 2015. But Dr. Thisted cites no evidence to support that assumption

[279] *See* Sections V.D.4 and VI.B.3, above.
[280] *See* Sections V.D.4 and VI.B.3, above.
[281] *See* Sections V.E and V.F, and VI.B.3, above.
[282] *See* Section VI.B.3, above.

and I do not know of any. Thus, I do not agree with Dr. Thisted's opinion, which is based on his unfounded assumption, that the results in Agarwal 2015 are unrepresentative of PH-ILD patients.

247. In ¶ 311 of his report, Dr. Thisted expresses an opinion which again confirms that he has applied the wrong legal standard to his analysis. Dr. Thisted states that "there was no expectation of success that the clinical trial required to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity." As I have explained, the legal standard for reasonable expectation of success does not require that a clinical trial "demonstrating" the claimed effect has already been performed.[283]

248. Concerning claims 2-3, 7-8, and 17-19, Dr. Thisted again discusses the topics of causality and that the prior art fails to "demonstrate" that the treatment effects observed in Agarwal 2015 were caused by inhaled treprostinil as opposed to some other cause. (Thisted Rpt., ¶¶ 313-315.) But as I noted above, these opinions apply the wrong legal standard, in two ways.[284] First, requiring that the prior art expressly demonstrate statistically significant treatment effects resulting from inhaled treprostinil uses the legal standard for anticipation, not obviousness. Secondly, the correct legal standard for obviousness requires only that a POSA would have had a reasonable expectation of success, based on the teachings of the prior art.[285] As I have detailed above and reiterate here, I agree with Dr. Channick's opinion that the express disclosure of a statistically significant improvement in exercise capacity in Agarwal 2015, especially when combined with all the other evidence available to a POSA, would have provided a POSA with that reasonable expectation of success.[286]

[283] *See* Section VIII.A, above.
[284] *See* Section VIII.D, above.
[285] *See* Section VIII.A, above
[286] *See* Section VI.B.4, above.

G. Response to Dr. Thisted's Opinion that Asserted Claims 4-5, 6, and 9-10 of the '327 patent are not rendered obvious by the '793 patent in combination with Agarwal 2015 and Saggar 2014.

249. In this section, I respond to ¶¶ 316-319 of Dr. Thisted's report.

250. Concerning claims 4-6 and 9-10 in the context of combining the '793 patent with Agarwal 2015 and Saggar 2014, Dr. Thisted simply repeats his opinions that Agarwal 2015 and Saggar 2014 do not disclose improved exercise capacity with inhaled and parenteral treprostinil, respectively, even though those reference do expressly disclose exactly that as I explained above.[287] Since Dr. Thisted's opinions in this regard simply repeat the same points he already made about Agarwal 2015 and Saggar 2014, I incorporate my responses to those arguments here.[288]

251. In ¶ 320, Dr. Thisted ends his report with a series of bullet point conclusions that repeat the opinions expressed in earlier paragraphs of his report. My responses to each of those opinions is provided in the foregoing sections of this report.

IX. RESPONSE TO DR. THISTED'S CRITIQUES OF DR. HILL'S REPORT

252. In ¶¶ 260-266 of his report, Dr. Thisted offers his opinions critiquing Section VI (¶¶ 131-173) of Dr. Hill's report, which describes the use of treprostinil by physicians, before 2020, as a therapy for Group 3 PH patients. I respond to those criticisms here.

253. Dr. Thisted dismisses the evidence of widespread use by physicians of inhaled treprostinil as a therapy for Group 3 PH patients as nothing more than "belief, personal experience, and biological plausibility." (*See* Thisted Rpt., ¶ 260.) However, Dr. Thisted's dismissive response to Dr. Hill's opinions unduly discounts that these practices were not based solely on belief, but are confirmed in the prior art reports that provided evidence of efficacy discussed in

[287] *See* Sections VIII.C and VIII.F, above.
[288] *See* Sections VIII.C and VIII.F, above.

Sections V.D, V.E, and V.F above. Dr. Thisted similarly does not acknowledge that this same widespread off-label use, and these prior art studies, is the body of evidence that persuaded UTC to perform a costly Phase III label extension study without first confirming efficacy in a smaller randomized Phase II trial, as I discuss in Sections V.E and V.F, above. Accordingly, Dr. Thisted fails to consider Dr. Hill's report in the wider context of all the evidence relating to the issue of reasonable expectation of success.

254. Dr. Thisted then proceeds to claim that medical history is "replete" with examples of failed therapies which were at one time believed to be effective, and then provides two such examples: ivermectin and flecainide. (*See* Thisted Rpt., ¶¶ 261-263.) As an initial matter I note that neither of these examples relates to treatments for pulmonary hypertension, but instead relate to the distinct clinical contexts of COVID-19 and sudden cardiac death. Further, I note that in Dr. Thisted's ivermectin example, the level of evidence supporting its use as a Covid therapy was limited to laboratory experiments and the hypotheses of certain physicians – quite different from the large body of evidence supporting the efficacy of treprostinil as a therapy for PH-ILD referenced above. More broadly, at best these two isolated examples shows only that success in drug development is not *guaranteed*. But as I have explained in this report, Dr. Thisted is applying the wrong legal standard for reasonable expectation of success when he insists that the scientific evidence must definitively demonstrate efficacy. Instead, I understand that under the correct legal standard a guarantee of success is not required – only that a POSA would have a reasonable level of expectation of success.

255. Dr. Thisted also again incorrectly relies on the early termination of the PERFECT trial of treprostinil in PH-COPD patients, even though this did not occur until Sept. 2022, well after the relevant time period for assessing a reasonable expectation of success, as I discussed

above in Section VIII.B. (*See* Thisted Rpt., ¶ 264.) I also note that Dr. Thisted appears to mischaracterize the published results of the PERFECT trial when he says that it gave "no indication of improvement in 6MWD." (*Id.*)

X. DR. THISTED'S OPINIONS ARE CONTRADICTED BY THE OPINIONS OF UTC'S EXPERT DR. WERTHEIM.

256. My response to Dr. Thisted's opinions is further impacted by the fact that Dr. Thisted takes positions that contradict or are inconsistent with opinions offered by UTC's other experts. As one example, as I detail further below, UTC's expert Dr. Wertheim relies on small sample size and single-arm studies in support of his opinions, which is inconsistent with Dr. Thisted's opinion that one cannot draw any inferences from studies of this type.

257. The inconsistencies in Dr. Thisted's report makes the interpretation of Dr. Thisted's opinions unclear, and he offers no explanation for how he reconciles his disparate opinions with those of UTC's other experts. I thus reserve the right to supplement my reply report to address any clarification or new information regarding opinions offered by UTC experts in this matter, and the right to further comment on the inconsistent and contradictory opinions of UTC's experts at trial.

XI. UTC'S EXPERT DR. WERTHEIM'S ANALYSIS OF A PURPORTED "CORRELATION" BETWEEN FVC AND 6MWD IS FLAWED

258. As noted above, for the purposes of my analysis of Dr. Thisted's opinions relating to anticipation and obviousness, I have been asked by counsel to assume that the '327 Patent is entitled to its claim to a priority date of April 17, 2020, even though I understand that Liquidia's expert Dr. Channick has opined that the '327 patent is not entitled to this earlier April 2020 priority date.[289] In response to those opinions, UTC's expert Dr. Wertheim offers his opinion that the

[289] *See* Channick Opening Report at ¶¶ 71-118.

claims of the '327 Patent are supported by the earliest-filed provisional application, the '810 Provisional Application filed on April 17, 2020.[290] In this section I offer my opinions in response.

259. Although Dr. Wertheim recognizes that the '810 Provisional Application does not contain any data at all about improvement of exercise capacity (such as through improvement in 6MWD), Dr. Wertheim opines that a POSA would still conclude that the inventors of the '327 Patent were in possession of their claimed methods for improving exercise capacity in a PH-ILD patient based on disclosures in the '810 Provisional relating specifically to FVC.[291] According to Dr. Wertheim, a POSA would understand that there is a "correlation" between FVC and 6MWD such that a POSA would conclude that the inventors possessed their claimed method of improving exercise capacity, based solely on FVC data.[292] Dr Wertheim relies on several scientific reports in support of those opinions.[293]

260. At the outset, I note the oddity that UTC's expert Dr. Wertheim, who is a clinician, was asked to opine on the interpretation of statistical significance and correlation, and that UTC's expert Dr. Thisted did not offer any opinions on this topic even though he is a qualified biostatistician. As I explain below, there are significant flaws with the manner in which Dr. Wertheim interprets the references that he contends show a correlation between FVC and improvement of exercise capacity as measured by data points such as 6MWD or peak VO_2.

261. In my opinion, Dr. Wertheim's analysis of these references, as well as the proposed correlation between forced vital capacity (FVC) and 6-minute walk distance (6MWD), is fundamentally flawed. First, the assumption that there is a direct and consistent relationship

[290] *See* Wertheim Rebuttal Report at ¶¶ 226-374.
[291] *See* Wertheim Rebuttal Report at ¶¶ 232-242.
[292] *See* Wertheim Rebuttal Report at ¶¶ 241-242.
[293] *See* Wertheim Rebuttal Report at ¶¶ 140-153, 240, 250, 272.

between these two measures overlooks the complexity of how they are influenced by different physiological mechanisms. FVC primarily reflects lung function, while 6MWD assesses a patient's overall functional status, including factors such as cardiovascular health, muscle endurance, and motivation, which can vary independently of pulmonary capacity. Furthermore, Dr. Wertheim's analysis fails to account for potential confounding factors, such as comorbidities or treatment variations, which could impact both FVC and 6MWD.

262. Thus, in my opinion, Dr. Wertheim's analysis of these references, and of a supposed correlation between FVC and 6MWD, is flawed. The references cited by Dr. Wertheim are related to studies conducted in patients with ILD, IPF, and CF. None of these papers address PH-ILD specifically, or patients that would fall within a sub-population of PH-ILD. In this case, it is not appropriate to take the results of one disease state and apply it to another. Dr. Wertheim also erroneously equates the existence of statistical significance with a meaningful correlation between variables. I explain the basis for my opinions further below.

A. Dr. Wertheim Assumes, Without Support, That Results in One Specific Patient Population, Apply to Another Different Patient Population

263. As detailed above in Section V.A, I understand from Dr. Channick that PH comprises a variety of conditions that affect the pressure in the blood vessels of the lungs.[294] As I have further noted, the PH caused by these conditions is commonly classified into five different groups, depending on, amongst other factors, underlying pathophysiology and clinical presentation. I further understand from Dr. Channick that interstitial lung disease ("ILD") is a distinct disease from PH.[295] ILD, a subset of WHO Group 3 PH, refers to a varied set of progressive lung diseases characterized by fibrosis (i.e., scarring and stiffening) of lung tissue.[296]

[294] *See* Channick Opening Report at ¶ 12.
[295] *See* Channick Opening Report at ¶ 18-19.
[296] *See* Channick Opening Report at ¶ 18.

ILD may include a range of underlying causes and conditions. These include pulmonary fibrosis ("PF"); idiopathic pulmonary fibrosis ("IPF"); connective tissue disease ("CTD"); and combined pulmonary fibrosis and emphysema ("CPFE").[297] Thus, these patients within WHO Group 3 would be characterized as PH-ILD patients.

264. The damage caused in the lungs by ILD, along with the reduced oxygen availability caused by ILD, often leads to increased pressure in the pulmonary circulation, resulting in PH.[298] Patients with PH-ILD suffer from pulmonary hypertension due to underlying lung disease. Thus, a POSA would not equate treatment of ILD or pulmonary fibrosis with treating PH-ILD because an ILD patient is not necessarily a PH-ILD patient.

265. While Dr. Wertheim himself recognizes that PH-ILD "is a disease of PH *and* ILD," he relies on publications concerning ILD/IPF/CF (without accompanying PH) without sufficiently explaining how the results of a study assessing patient outcomes in one disease state necessitate achieving the same results in a population in a different disease state.[299] Of the 12+ studies that Dr. Wertheim describes in his report as indicative of "a correlation between FVC and known measures of exercise capacity," none were meant to study the relationship between these measures in the PH-ILD population that is subject of the '810 Provisional Application.[300]

266. In fact, the Nishiyama 2016 publication cited by Dr. Wertheim notes that discrepancies in the study arose seemingly due to "differences in patient characteristics" and that "[o]nly 4% of patients had pulmonary hypertension."[301] The publication further explains that "some patients with pulmonary hypertension could have been excluded" from the study because

[297] *See* Channick Opening Report at ¶ 18.
[298] *See* Channick Opening Report at ¶ 19.
[299] Wertheim Rebuttal Report at ¶ 138.
[300] Wertheim Rebuttal Report at ¶ 240.
[301] UTC_PH-ILD_220980 at UTC_PH-ILD_220982.

"patients with long-term oxygen therapy . . . could not discontinue[] their oxygen apparatus at the time of 6MWT[.]"[302] The publication's reasoning for possible exclusion of PH-ILD, suggests that other studies focusing on ILD may suffer from the same exclusion of PH-ILD patients.

267. It is improper to extrapolate the results from studies assessing the relationship between FVC and exercise capacity in patients suffering from ILD/IPF/CF to conclude that the same relationship between variables would be experienced in PH-ILD patients. Dr. Wertheim provides no explanation as to why results in the ILD patient populations which were the subject of each of the publications he cites should apply to the subset of PH-ILD patients in the '327 patent. Thus, the results of these studies observed in the greater ILD population may not accurately reflect what would be seen in PH-ILD patients specifically.

B. Dr. Wertheim's References Do Not Evidence a Meaningful Correlation between FVC and 6MWD

268. Even adopting Dr. Wertheim's view that studies of patients in a different disease state are nevertheless relevant to the PH-ILD population, Dr. Wertheim's statement that "numerous disclosures would have been available to a POSA demonstrating that changes in FVC were correlated with changes in exercise capacity[,]" exaggerates the clinical significance of the publications he cites.[303]

269. Dr. Wertheim admits that "a POSA would take care not to over-interpret the observation findings discussed in [the studies he cites], as they do not demonstrate causality."[304] However, Dr. Wertheim does mischaracterize these references when he opines that "numerous disclosures would have been available to a POSA demonstrating that changes in FVC were correlated with changes in exercise capacity," and "[a] POSA would have particularly appreciated

[302] UTC_PH-ILD_220980 at UTC_PH-ILD_220982.
[303] Wertheim Rebuttal Report at ¶ 140.
[304] Wertheim Rebuttal Report at ¶ 153.

the importance of this correlation in the context of PH-ILD, a patient population with known lung pathology, and thus lower baseline FVC values as compared to PAH patients."[305] As I explain further below, a POSA would not understand the publications cited by Dr. Wertheim to demonstrate a clinically meaningful correlation between FVC and exercise capacity, nor would the publications support a POSA's "particular[] appreciate[ion]" of any purported "correlation in the context of PH-ILD" because, as I have previously noted, the studies were not conducted in the PH-ILD patient population.

270. A POSA would have understood that data can evidence a weak or moderate correlation to a statistically significant degree. In other words, data showing a statistically significant result in the context of a test for correlation such as a Pearson test, do not mean that the underlying correlation is strong. Instead, statistical significance of such results indicates only that the detected correlation is statistically unlikely to be due to chance. It does mean that the strength of the correlation is strong. For example, several of the studies relied on by Dr. Wertheim report correlation data as a Pearson correlation coefficient, or "r-value." Such "r-values" report correlation in values ranging from -1 to +1. An r-value of +1 indicates a very strong correlation, while an r-value of 0 indicates no correlation at all.

271. Thus, correlation data that is statistically significant does not necessarily mean that a correlation is strong, in fact it might be quite weak as is the case for several of Dr. Wertheim's references as discussed below. A POSA would take care to not conflate statistical significance with meaningful correlation and would instead interpret the findings in Dr. Wertheim's publications as demonstrating that minimal conclusions can be drawn as to the relationship between FVC and exercise capacity. I discuss each of Dr. Wertheim's cited references below.

[305] Wertheim Rebuttal Report at ¶ 140.

1. Swigris 2010

272. For example, Dr. Wertheim states that Swigris 2010 discloses a "positive relationship between 6MWD and FVC" such that a POSA would understand "that in IPF patients whose percent predicted FVC improves from baseline to 6 months, there is associated improvement in 6MWD—and in patients whose percent predicted FVC worsens, their 6MWD tends to decline."[306] Dr. Wertheim notes that the relationship between FVC and 6MWD found in Swigris 2010 was statistically significant over a period of six months.[307] However, Dr. Wertheim fails to address the magnitude of the changes in 6MWD relative to the minimal important different (MID). MID is the smallest change in a treatment outcome that a patient considers important, and the objective of the Swigris 2010 study was to examine changes over time in 6MWD and to estimate the change in distance that constitutes the MID in patients with IPF.[308]

2. Wallaert 2011

273. As Dr. Wertheim notes, Wallaert 2011 indicates that with respect to sarcoidosis, FVC "accounts for up to 17% of the variation between VO_2 peak in the study population."[309] Dr. Wertheim substitutes "up to 17%" for what the publication describes as "only 17%."[310] This value indicates that while FVC was found to be a significant predictor of VO_2 peak, FVC explained ***only*** 17% of VO_2 alteration. The remaining 83% of variation is unexplained, indicating that other factors (e.g., ventilation-perfusion mismatch, muscle deconditions, or other pulmonary or cardiovascular factors) may play a more substantial role in exercise intolerance in sarcoidosis patients. Thus, this paper indicates only a very weak correlation, at best, between FVC and VO_2

[306] Wertheim Rebuttal Report at ¶ 145.
[307] Wertheim Rebuttal Report at ¶ 145.
[308] *See* UTC_PH-ILD_221336.
[309] Wertheim Rebuttal Report at ¶ 146.
[310] *See* UTC_PH-ILD_221552 at UTC_PH-ILD_221558.

peak.

3. du Bois 2010 & du Bois 2011

274. Both du Bois 2010 and du Bois 2011 disclose a statistically significant relationship between 6MWD and percent predicted FVC.[311] However, neither publication discloses a strong correlation between the two variables. In fact, the correlation coefficients are low (0.12 and 0.22), which suggests a weak relationship between the two variables at best. This means that a significant amount of variation in 6MWD is not explained by FVC. While both studies report statistically significant p-values (<0.001), this does not necessarily imply that the correlation is meaningful from a clinical perspective. Instead, the weak correlation coefficients indicate that changes in FVC are only weakly associated with changes in 6MWD, which may not be sufficient for using these metrics interchangeably in clinical settings. Clinically meaningful relationships typically require stronger correlations or more substantial effect sizes. Indeed, the du Bois 2010 publication notes that "6MWD was weakly correlated with measures of physiologic function and health-related quality of life."[312] As noted in the du Bois 2010 Study Protocol, FVC is one such measure of physiologic function.[313] Similarly, du Bois 2011, as demonstrated in Table 2 of the publication, found that FVC and 6MWD were only weakly correlated.[314]

4. Nathan 2015

275. Nathan 2015 is a *post-hoc* analysis of the CAPACITY trial.[315] This means that the relationships between variables were not pre-specified. Dr. Wertheim notes that Nathan 2015 reports a "statistically significant trend" but does not provide any specifics on the statistical

[311] *See* UTC_PH-ILD_221604, UTC_PH-ILD_221611.
[312] UTC_PH-ILD_221604 at UTC_PH-ILD_221604.
[313] UTC_PH-ILD_221604 at UTC_PH-ILD_221605.
[314] UTC_PH-ILD_221611 at UTC_PH-ILD_221613.
[315] *See* Wertheim Rebuttal Report at ¶ 148.

metrics, such as correlation coefficients, p-values, or effect sizes. Nor does Dr. Wertheim discuss the magnitude of the correlation or the clinical implications of the results. As I previously noted, a trend can be significant without being strong or clinically meaningful and weak correlations may not offer much predictive value in clinical practice. Table 2 in the Nathan 2015 publication shows a correlation coefficient of 0.111 and 0.289 for 6MWD and FVC percent predicted for baseline and 48-week change respectively.[316] As noted in the publication, "[a]ssociations were determined using Spearman correlation coefficients; the strength of the correlation was determined based on Cohen's criteria, under which an absolute value of a coefficient >0.5 is indicative of a large correlation, 0.5-0.3 of a moderate correlation, 0.3-0.1 of a weak correlation, and <0.1 of a trivial correlation."[317] Thus, while Nathan 2015 demonstrates statistical significance between 6MWD and FVC percent predicted, this correlation was "weak" at best and borderline "trivial."

5. Oldham 2018

276. Oldham 2018 refers to a study which was conducted using "network analysis."[318] While Dr. Wertheim describes network analysis as a novel way to characterize relationships, there are potential limitations and challenges to this method which he does not address. Network analysis can be powerful, but also presents a risk of overfitting, misinterpretation of correlations as causal relationship, or failure to account for all relevant variables. Without more context, it is unclear how robust and reliable these findings are. Moreover, the metaphor of "friendship" to characterize the relationship between FVC and VO_2 peak oversimplifies complex biological relationships. Moreover, while the study successfully predicted hospitalization risk using FVC as a predictor, the clinical relevance of this finding is not discussed in detail.

[316] UTC_PH-ILD_220929 at UTC_PH-ILD_220931.
[317] UTC_PH-ILD_220929 at UTC_PH-ILD_220931.
[318] *See* Wertheim Rebuttal Report at ¶ 149.

6. Nishiyama 2016

277. Dr. Wertheim states that "Nishiyama 2016 discloses Pearson correlation coefficients between 6MWT outcomes and various parameters including absolute FVC (p=0.00005) and percent predicted FVC (p=0.0007) which are statistically significant."[319] However, while the p-values reported suggest statistical significance, as previously noted, a relationship can be statistically significant and simultaneously weakly correlative. The Pearson's correlation coefficient describing the relationship between FVC and 6MWD in Nishiyama 2016, denoted as "r", is suggestive of a weak correlation at best in Nishiyama's data. As noted in Table 3 of Nishiyama 2016, the correlation coefficients for FVC and percent predicted FVC, were reported as 0.49 and 0.39 respectively.[320] The square of the correlation coefficient, known as the coefficient of determination, describes how much variance in one variable is explained by the variance in another variable within a linear regression model. The coefficients of determination for FVC and percent predicted FVC disclosed in Nishiyama 2016 are 0.24 and 0.15 respectively.[321] These values indicate that 76% of variation in FVC is not explained by variation in 6MWD and 85% of variation in percent predicted FVC is not explained by variation in 6MWD – showing that Nishiyama 2016 does not provide compelling evidence of a correlation between FVC and 6MWD.

7. Brown 2018

278. Dr. Wertheim, quoting Brown 2018, states that "'test validity was demonstrated by associations in the expected direction between 6MWT distance and various physiologic measures, including percent predicted FVC[,]'" which "would have directed a POSA to pay attention to the correlation between FVC and 6MWD as a means to 'confirm meaningful changes in other clinical

[319] Wertheim Rebuttal Report at ¶ 150.
[320] *See* UTC_PH-ILD_220979 at UTC_PH-ILD_220983.
[321] *See* UTC_PH-ILD_220979 at UTC_PH-ILD_220983.

trial parameters.'"[322] However, Brown 2018 does not provide specific details on the strength of the purported correlation, and it is thus difficult to assess whether the reported associations are clinically meaningful. As the Brown 2018 publication notes, a *post-hoc* analysis of data from the INSPIRE trial showed that "the 6MWT distance and 24-week change in 6MWT distance were closely associated with 1-year mortality despite ***relatively weak correlations between 6MWT distance and various measures of pulmonary function***[.]"[323] And, as further noted, the weak correlation "suggests that 6MWT may assess a separate, clinically significant domain of the disease process and provide additional information regarding prognosis." (UTC_PH-ILD_220101 at UTC_PH-ILD_22102.)

8. Noble 2011

279. Dr. Wertheim opines that because Noble 2011 (The CAPACITY Trial) "demonstrated that pirfenidone reduces the decline in FVC, progression-free survival, and mean change in 6MWD vs. placebo[,]" FVC and 6MWD are therefore correlated.[324] As with the aforementioned studies, Dr. Wertheim fails to assess the strength of any correlation exhibited between FVC and 6MWD. Moreover, the CAPACITY Trial itself was not meant to test the strength of the correlation between FVC and 6MWD, but rather the benefit risk profile of pirfenidone.[325]

9. The ASCEND Trial

280. The ASCEND trial, like CAPACITY, was not aimed at assessing the strength of any correlation between 6MWD and FVC.[326] The purpose of ASCEND was to evaluate whether

[322] Wertheim Rebuttal Report at¶ 151.
[323] UTC_PH-ILD_220101 at UTC_PH-ILD_22102.
[324] Wertheim Rebuttal Report at ¶ 141.
[325] *See* UTC_PH-ILD_220986.
[326] *See* UTC_PH-ILD_220818.

pirfenidone reduced disease progression, as measured by the decline in FVC, in patients with IPF.[327] Researchers found that pirfenidone reduced the "proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died[,]" in addition to demonstrating a relative increase in the proportion of patients with no decline in FVC.[328] Pirfenidone also reduced the decline in 6MWD.[329] While the ASCEND trial demonstrated statistically significant improvements in clinical outcomes for patients receiving pirfenidone versus the placebo, neither the cited publications nor Dr. Wertheim address the strength of any purported relationship between 6MWD and FVC.

10. Fell 2009

281. As Dr. Wertheim notes, the patients in Fell 2009 "were referred for enrollment in study protocols for suspected IPF based on typical symptoms, physiologic findings, and radiographic findings[,]" and were thus not in the PH-ILD patient population that is the subject of the '327 patent.[330] The authors of the study even noted that, among the limitations of the study was the fact that patients "were not evaluated for the presence of pulmonary hypertension[,]" which "has been shown to be an important predictor of mortality in IPF [], although its presence does not universally portend a poor outcome[.]"[331] The purpose of the Fell 2009 study was to assess the predictive value of VO_2 max in all cause mortality, not to assess the correlation between exercise capacity and FVC.[332] I also note that Dr. Wertheim omits the statement made by the authors of Fell (2009), who observed that "[i]n prior studies of patients with interstitial lung

[327] *See* UTC_PH-ILD_220818.
[328] *See* UTC_PH-ILD_220818.
[329] *See* UTC_PH-ILD_220818.
[330] Wertheim Rebuttal Report at ¶ 144.
[331] UTC_PH-ILD_220279 at UTC_PH-ILD_220282.
[332] *See* UTC_PH-ILD_220279.

disease, VO2 max correlated poorly with measures of lung volume."[333] This omission is significant, as it directly challenges the idea that, by 2020, a POSA would have reasonably believed there was any correlation between these variables.

11. Pastré 2014

282. Dr. Wertheim cites Pastré 2014, a study of patients with cystic fibrosis (CF) to support his correlation argument, noting that "[e]ven in populations without ILD or a high risk of PH, percent predicted FVC is significantly associated with exercise capacity[.]"[334] As I have explained above in Section XI.A, it is improper to take the results of a study conducted in one patient population and conclude that they would automatically apply to another. Dr. Wertheim seems to conclude that his position is strengthened by the results demonstrated in Pastré 2014, though results from a study of CF patients would not communicate to a POSA that the same relationship between variables exists in those experiencing an entirely different disease. Moreover, Dr. Wertheim argues that the Pastré 2014 results indicate a "robust" association between percent predicted FVC and VO_2 peak.[335] I disagree. The correlation coefficient reported in Pastré 2014, r=0.69, is not supportive of a strong relationship between percent predicted FVC and VO_2 peak. As I have previously explained, a POSA would understand that the coefficient of determination, an r^2 value of 0.48 in this case, means that 52% of the variation in percent predicted FVC is not explained by variation in VO_2 peak.

12. Carter 2003

283. As with Pastré 2014, Dr. Wertheim references Carter 2003 in a footnote to support his analysis that the correlation is further supported by studies of patients who do not have PH-

[333] UTC_PH-ILD_220279 at UTC_PH-ILD_220279.
[334] Wertheim Rebuttal Report at ¶ 152.
[335] Wertheim Rebuttal Report at ¶ 152.

ILD.[336] For the same reasons as I have already noted, Carter 2003 would not communicate to a POSA that FVC and exercise capacity are variables that can be used interchangeably. Moreover, and as Dr. Wertheim notes in his footnote, Carter 2003 "identified anthropometric and physiologic variable[s] that can influence a patient's ability to engage in physical work."[337] The statement that "[t]he addition of DCLO, FVC, MIPs, weight, and age improved the predictability of the model from an R^2 equal to .42 to slightly greater than 79%[,]" does not imply that FVC alone was responsible for the improved predictability. Instead, the statement describes the combined contribution of all the variables to the model's enhanced performance.

13. Singh 2014

284. Dr. Wertheim cites Singh 2014 as yet another publication "linking changes in FVC to changes in exercise capacity[.]"[338] Singh 2014 is a publication which reviews studies that report the evaluation or use "the 6-min walk test (6MWT), incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) in adults with chronic respiratory disease."[339] As with the other cited publications, Dr. Wertheim fails to explain how results in one patient population should apply to entirely different group of patients. An additional concern with Singh 2014 is that, as a "systematic review," the reference does not provide sufficient detail to critically assess the reliability, applicability, and significance of the individual studies included.

C. Statistically Significant Differences in One Variable, Tested Between Treatment and Placebo Populations, Do Not Automatically Translate Into Statistically Significant Improvements in Another Variable, Tested Within the Treatment Population

285. With respect to claims 9 and 10 of the '327 patent, Dr. Wertheim argues that the

[336] Wertheim Rebuttal Report at ¶ 152.
[337] UTC_PH-ILD_220157 at UTC_PH-ILD_220161.
[338] *See* Wertheim Rebuttal Report at ¶ 240.
[339] Singh 2014 at 1447.

percent predicted FVC values reported in the specification would "be sufficient for a POSA to understand that the inventors possessed a method of achieving a statistically significant improvement in FVC" as required by the claim.[340] I do not agree with Dr. Wertheim's assumption that statistically significant differences in percent predicted FVC, tested between populations, demonstrate statistically significant improvements in absolute FVC, tested within a population.

286. At the outset, it is my opinion that Dr. Wertheim's opinion mischaracterizes the results provided in Tables 1-3 of the '327 patent. The tables show statistically significant results in FVC in the population receiving treatment versus the patients who received a placebo. This communicates to a POSA that there was a statistically significant ***difference*** in populations (treatment v. placebo) as opposed to demonstrating an ***improvement*** over baseline in the treatment group.

287. Moreover, absolute FVC and percent predicted FVC are two different measurements. As Dr. Wertheim notes in his report, "[w]hen FVC is measured clinically, the resulting data is typically expressed in one of two ways: 'absolute FVC' and 'percent predicted FVC.'"[341] Dr. Wertheim goes on to explain that "Absolute FVC is the raw measurement from testing the patient and is reported in volume units[,]" whereas "Percent Predicted FVC compares this volume to what a patient's optimal FVC should be based on their demographics and is reported as a percentage."[342] As Dr. Wertheim notes, "[t]he demographic factors used to calculate percent predicted FVC include age, sex, height, arm span, and as of April 2020, race/ethnicity[.]"[343] The demographic factors that are used to calculate a patient's optimal FVC, and thus percent predicted

[340] Wertheim Rebuttal Report at ¶ 381.
[341] Wertheim Rebuttal Report at ¶ 65.
[342] Wertheim Rebuttal Report at ¶ 65.
[343] Wertheim Rebuttal Report at ¶ 65.

FVC, are not static. For example, a patient's optimal FVC will change as they age. Therefore, a patient's percent predicted FVC could potentially increase, as the patient's optimal FVC decreases, while the patient's absolute FVC actually decreases. These measurements should not be used interchangeably.

288. Statistical significance indicates whether we should reject the null hypothesis but does not convey the magnitude or direction of the treatment effect. A significant result simply suggests that an observed difference is unlikely to be due to chance, without specifying how large or meaningful that difference is. Claim 10 of the '327 patent depends from claim 9.[344] I understand from Dr. Channick that this means that claim 10 requires that the inventors possessed both a method of achieving a statistically significant improvement in FVC and that the patient's FVC increased "by at least 20 ml after 8 weeks, 12 weeks, or 15 weeks of the administering."[345] Even if one were able to show that the patient experienced a statistically significant improvement in FVC, this would not mean that the patient experienced the additional level of improvement as required in claim 10. The converse is also true. Even if results demonstrated improvement at the levels disclosed in claim 10, this would not automatically equate to the statistically significant improvements as required by claim 9.

289. As confirmed by Dr. Nathan, one of UTC's expert witnesses and a member of the steering committee for INCREASE, a subset of patients in the INCREASE study demonstrated significant improvements in percent predicted FVC but not in absolute FVC.[346] The magnitude of the percent predicted FVC improvement was 1.1%.[347] I understand that UTC is now conducting

[344] '327 patent, claim 10.
[345] '327 patent, claim 10.
[346] Nathan Depo. Tr. at 204:23-205:6.
[347] NEJM Publication at UTC_PH-ILD_010825 (Table S6).

the TETON study to see whether patients actually show an improvement in FVC.[348] In my opinion, this serves to further support the fact that statistically significant results in percent predicted FVC cannot be assumed to mean that there would be statistically significant results in absolute FVC.

XII. RESERVATION OF RIGHTS

290. This report is based on information currently available to me. I reserve the right to continue, update, and expand my investigation and analysis in a supplemental report if additional documents, deposition transcripts, or any other information is produced by UTC. I reserve the right to respond to any matters raised by Liquidia, or any opinions or conclusions of any expert, by relying on documents or other information that is additional to the information considered and cited herein. I further reserve the right to prepare exhibits to summarize and demonstrate my testimony at trial, and to supplement my opinions as permitted by any Court order.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: February 21, 2025

Stephan Ogenstad, Ph.D.

[348] Nathan Depo. Tr. at 117:12-118:17.

EXHIBIT 7

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)
Plaintiff,	)
vs.	) C.A. No. 23-975 (RGA)(SRF)
LIQUIDIA TECHNOLOGIES, INC.,	)
Defendant.	)

VIDEOTAPED DEPOSITION OF STEPHAN OGENSTAD, Ph.D.

(Taken by Plaintiff)

Raleigh, North Carolina

Thursday, March 20th, 2025

Reported by:

Amy A. Brauser, RPR, RMR, CRR

Job No.: 10334

correct?

A. That's correct.

Q. And you don't contend that you are a POSA under UTC's definition, do you?

A. I'm not.

Q. Okay. And then similarly, you see that there's a Liquidia POSA definition, correct?

A. Yes.

Q. And you do not contend that you are a POSA under Liquidia's POSA definition, correct?

A. No, because I'm not a clinician.

Q. And so you're not a POSA, correct?

A. Not as a clinician.

Q. And not as defined by Liquidia, correct?

A. Well, to be a POSA, I understand that you need to have a medical degree and you have a specialty in pulmonary and cardiology and that you for at least two years, you have experience of treating patients. I've never done that.

Q. Understood.

And so you're not a POSA under Liquidia's definition, correct?

A. That's correct.

Q. Do you understand that -- well, strike

regarding the opinions in your report?

A. If I'm asked, yes.

Q. And there are no opinions that are not in your report that you would intend to provide at trial, correct?

A. Not at the moment.

Q. A significant portion of your report is dedicated to relying on Dr. Channick's opinions, correct?

A. Yes, a lot. Not all, but a lot.

Q. And where you're relying on Dr. Channick's opinions, you're not forming your own opinions, you're relying on his opinions, correct?

MR. KNAUSS: Object to the form.

THE WITNESS: Well, that's not true. I rely on his expertise, but I form my own opinion.

BY MR. BURROWBRIDGE:

Q. I understand. Maybe it was a bad question.

Let me ask you this: You believe that Dr. Channick's -- excuse me. You believe that Dr. Channick's opinions are accurate, correct?

A. It seems to be very truthful what he's

writing. So I do that. I think he's very qualified.

Q. Are you aware that Dr. Nathan is an expert in this deposition?

A. Doctor?

Q. Dr. Nathan.

A. Yeah.

Q. Do you believe he's qualified as well?

A. I think so.

Q. You never cited Dr. Nathan in your expert report, correct?

A. I didn't? I don't remember. If you found I did, can you point me to the place?

Q. I'll represent to you that I have not seen anywhere in your report where you cite to Dr. Nathan.

A. Yeah, I don't remember.

Q. Okay. Do you remember anyplace where you rely on Dr. Nathan's opinions?

A. I would need to look through my report. If you have found it, please let me know.

Q. I haven't found it.

A. Oh, okay.

Q. And I don't think you have.

A. Okay.

Q. But what I think doesn't matter quite as much as what you think because you're the expert.

A. No. It's a thick report.

Q. I understand. I'm just -- you know, I guess I'm trying to understand if you can remember any instance where you relied on Dr. Nathan's opinion about something.

A. I don't remember, right.

Q. Okay. Do you ever remember considering Dr. Channick's opinion of something and Dr. Nathan's opinion about something and kind of assessing which one you think is accurate?

A. Well, I've taken them at face value. I think they are both accurate.

Q. Well, you took Dr. Nathan's opinions at face value, correct?

A. Yes.

Q. You did not take Dr. Nathan's opinions at correct value, correct?

A. You repeated that.

Q. Yeah. I'll fix that.

You took Dr. Channick's opinions at face value, correct?

A. Yes.

Q. You did not take Dr. Nathan's opinions at face value, correct?

A. I don't know.

Q. You would agree if you didn't cite to Dr. Nathan, you didn't take his values -- or sorry.

You would agree that if you didn't cite to Dr. Nathan in your report, you did not rely on Dr. Nathan's opinions, correct?

A. Did you finish your question?

Q. I did.

A. Oh, you did. Okay.

I haven't mentioned it here. I don't remember if I relied on it. But as you said, you can find it in the report.

Q. Okay. So again, a lot of your report refers to Dr. Channick's opinions. Was it your decision to rely on Dr. Channick's opinions for large portions of your report?

A. It's my decision, yes, but I got the report from counsel.

Q. Uh-huh.

At trial, do you intend to testify with regard to Dr. Channick's opinions?

A. Maybe. If I'm asked to.

Q. So you would feel qualified to stand up

EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 23-975 (RGA)(SRF) **HIGHLY CONFIDENTIAL**

REPLY EXPERT REPORT OF DR. RICHARD CHANNICK

course of treatment and dropped out. In INCREASE, baseline characteristics were assessed for 163 patients—40 patients discontinued treprostinil prematurely with 33 patients discontinuing from study participation entirely.[181]

85. Dr. Thisted further suggests that Parikh 2016 "is at least subject to all limitations associated with . . . uncontrolled nonrandomized single-arm studies,"[182] which include the natural course of disease recovery or clinical therapy other than treprostinil biases.[183] I previously addressed Dr. Thisted's argument in paragraph 59.

V. PRIORITY DATE

86. As noted in his Curriculum Vitae ("CV"), Dr. Bradley Wertheim is an attending physician at Brigham Women's Hospital (BWH), working in the inpatient BWH Pulmonary Vascular Disease (PVD) service or PVD clinic.[184] Dr. Aaron Waxman, who was an expert witness for UTC in the prior proceedings involving U.S. Patent No. 10,716,793, has been the Director of BWH's Pulmonary Vascular Disease Program since 2009.[185] In addition to his work in Dr. Waxman's PVD program, Dr. Wertheim trained under me as an intern and resident between 2011-2014.

87. Dr. Wertheim argues that claims 1, 2, 6-11, and 14-16 of the '327 patent are entitled to a priority date of April 17, 2020, as this date corresponds to the filing date of the '810 provisional and because a POSA reading the disclosures of the '810 provisional would understand (1) that the inventors were in possession of the inventions described in each of claims 1, 2, 6-11, and 14-16 of the '327 patent (satisfying written description); and (2) that the methods described in each of those

[181] NEJM Publication (UTC_PH-ILD_010790) at UTC_PH-ILD_010794 (Fig. 1).
[182] Thisted Rebuttal Report at ¶ 153.
[183] *Id*. at ¶¶ 63-70.
[184] *See* Wertheim Rebuttal Report at Ex. 1 (Wertheim CV).
[185] *See* Wertheim Rebuttal Report at Ex. 1 (Wertheim CV).

claims could be performed without undue experimentation (satisfying enablement).[186] This opinion is based on Dr. Wertheim's belief that the '810 provisional discloses the administration of inhaled treprostinil to PH-ILD patients to improve the patient's exercise capacity.[187] However, it is my opinion that in reaching this conclusion, Dr. Wertheim improperly equates the treatment of ILD with the treatment of PH-ILD and relies on a purported correlation between FVC and 6MWD, which is not enough to show that the '810 provisional supports the full scope of claim 1 of the '327 patent as well as 2, 6-11, and 14-16, which depend from claim 1.

A. Inventor Testimony Regarding "Possession" of the Invention

88. [redacted].[188] Further, in my Opening Report on priority, I noted that the inventors indicated that they had not invented the '327 patent claims until the results of the INCREASE study were revealed.[189] Dr. Wertheim has responded by stating that it is "unclear to [him] how inventor testimony given in 2024—of which a POSA would have no knowledge—would be relevant to how a POSA would interpret the '810 Provisional Application."[190] Dr. Werthheim side-steps the issue. If the inventors confirm that they could not have invented the '327 patent claims until they saw actual data from the INCREASE study, then it follows a POSA could not conclude these same inventors were in possession of a method of improving the exercise capacity of a PH-ILD patient by administering inhaled treprostinil based on the '810 application, which did

[186] Wertheim Rebuttal Report at ¶ 226. Dr. Wertheim does not address priority date with respect to claims 3-5 and 17-19 of the '327 patent.
[187] *Id*. at ¶ 229.
[188] *See* Channick Opening Report at ¶¶ 83-85.
[189] *Id*. at ¶ 72.
[190] Wertheim Rebuttal Report at ¶ 256.

not contain this critical data. Dr. Wertheim's opinion on priority completely contradicts the position UTC and the inventors have taken.

B. Dr. Wertheim Improperly Assumes Equivalence Between Treatment of ILD and PH-ILD

89. The '810 provisional application, entitled "TREATMENT FOR INTERSTITIAL LUNG DISEASE[,]" includes three independent claims, none of which claim a method for treating PH-ILD.[191] [redacted].[192] Although Tables 2 and 3 make reference to "Mixed Model Repeated Measurement for PH-ILD Etiology of" IPP and IPF, respectively, looking at Example 1 of the '810 application, it does not provide inclusion or exclusion criteria one would expect to see for a patient deemed to have PH-ILD, such as PVR, PAP, or pulmonary capillary wedge pressure.[193] Even Dr. Wertheim acknowledges that Example 1, which he argues demonstrates examination of PH-ILD patients, "make[s] reference to the treatment of 'ILD,'" not PH-ILD.[194] I note this because Dr. Nathan, in his Rebuttal Report, contends that neither Agarwal 2015 nor Faria-Urbina 2018 treated PH-ILD patients because the PH was "out of proportion" to ILD.[195] As discussed above, UTC's experts take inconsistent positions, making it difficult to fully understand what UTC and its experts will ultimately present to the Court. But if UTC follows Dr. Nathan's view regarding the disclosure of Agarwal 2015 and Faria-Urbina 2018, then Dr. Wertheim cannot point to Example 1 of the '810 application and its

[191] *See* '810 provisional application (UTC_PH-ILD_069472) at UTC_PH-ILD_069474 ([0001]).
[192] Smith Depo. Tr. at 72:8-18 ("[redacted].
[193] *See* '810 provisional application (UTC_PH-ILD_069472) at UTC_PH-ILD_069495-501 (Example 1, [0080]-[0088]).
[194] Wertheim Rebuttal Report at ¶ 230.
[195] Nathan Rebuttal Report at ¶¶ 222-223.

results to support his opinion that the inventors were in possession of the invention claimed in the '327 patent claims.

C. Dr. Wertheim Improperly Reads INCREASE into the '810 Provisional Application

90. Dr. Wertheim supports his argument that the '810 provisional discloses the administration of inhaled treprostinil to treat PH-ILD patients, by opining that "a POSA would recognize the clinical results reported in Example 1 as coming from UTC's INCREASE study," though the '810 provisional makes no mention of INCREASE.[196] It is my understanding from counsel that a determination the written description has been demonstrated, for the purpose of priority, has to be assessed from what is disclosed to a POSA in the specification of the application itself, not information outside the specification. Dr. Wertheim also notes in the legal standards section of his report that he "understand[s] that the specification must disclose sufficient information to allow the POSA, in view of [] his or her knowledge and experience, to draw general conclusions consistent with the scope of the claims."[197] Thus, Dr. Wertheim's reliance on the INCREASE study, which is not mentioned at all in the '810 application to support his opinion is improper and cannot be used by a POSA to determine whether the inventors were in possession of the '327 patent claims.

91. Nonetheless, Dr. Wertheim's assertion that a POSA would consult the INCREASE study when reviewing the claims of the '810 provisional application is without support. First, the '810 provisional makes no mention of INCREASE. Indeed, at the time the '810 provisional was filed, [redacted].[198]

[196] Wertheim Rebuttal Report at ¶ 230.
[197] *Id*. at ¶ 56.
[198] *See* UTC_LIQ00078069 at UTC_LIQ00078072 [redacted] *Id*.

92. Second, the assumption that a POSA would consult INCREASE, when there is no mention of INCREASE, runs contrary to Dr. Nathan's opinion that claim 1 of the '327 patent is not anticipated by the February 2020 press release because "the February 2020 Press Release does not provide all of the information the POSA would want to review."[199]

93. Unlike the '810 provisional, INCREASE is explicitly mentioned in the 2020 Press Release entitled "United Therapeutics announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints."[200] The 2020 Press Release discloses the results of the INCREASE Study, including that "[t]yvaso increased six-minute walk distance by 21 meters versus placebo (p=0.0043, Hodges-Lehmann estimate) after 16 weeks of treatment[,]"[201] which Dr. Smith confirmed meant that there was a "statistically significant difference between placebo and Tyvaso in six-minute walk distance."[202] Certainly, if Dr. Nathan opines that a POSA would ignore the INCREASE study itself, despite the fact that the entire 2020 Press Release is about that study, then Dr. Wertheim cannot be correct that a POSA would conduct an investigation to find INCREASE when the '810 application makes no mention of it. Dr. Wertheim declined to address this inconsistency.

D. An Alleged Correlation Between Endpoints is Not Sufficient to Show the Inventors Were in Possession of the '327 Patent Invention

94. Dr. Wertheim argues that the '810 provisional application "directly communicates to the POSA that the method of treatment it describes will result in an improvement in exercise capacity."[203] Dr. Wertheim finds his purported support for this argument in paragraph [0009] of

[199] Nathan Rebuttal Report at ¶ 365.
[200] United Therapeutics, *United Therapeutics Announces INCREASE Study of Tyvaso® Meets Primary and All Secondary Endpoints*, https://ir.unither.com/press-releases/2020/02-24-2020-161749814 (Feb. 24, 2020) ("Feb. 2020 Press Release") (UTC_LIQ00063612).
[201] Feb. 2020 Press Release at UTC_LIQ00063612.
[202] Smith Depo. Tr. at 214:11-216:10.
[203] Wertheim Rebuttal Report at ¶ 232.

the '810 provisional application which states that the methods described will result in an "improvement in symptoms such as shortness of breath and fatigue."[204] Dr. Wertheim further opines that "improvements in symptoms associated with exercise capacity are echoed in claims 9-11 of the '810 Provisional Application," because they cover "reductions in fatigue and/or shortness of breath."[205] Dr. Wertheim also relies on Example 1 of the '810 provisional application, similarly arguing that a correlation between the clinical endpoints disclosed in Example 1 and the '327 patent's claimed "improvements in exercise capacity" demonstrate that a POSA would understand the '810 provisional application to cover improvements in exercise capacity in PH-ILD patients.[206]

95. Importantly, Dr. Wertheim does not point to any actual results demonstrating any improvement in shortness of breath, 6MWD, or any other parameter supporting an improvement in exercise capacity. [redacted][207] [redacted]

[redacted] *Id*.
[205] *Id*. at ¶ 233.
[206] *Id*.
[207] *See e.g.*, Nathan Depo. Tr. at 43:2-22 [redacted]; Tapson Depo. Tr. at 155:13-156:6; *see also* Nathan Rebuttal Report at ¶¶ 741-742.

E. Publications Purporting to Establish a Correlation Between FVC and Exercise Capacity Do Not Support a Claim to Priority to the April 2020 Date of the '810 Provisional Application

96. Relying on "literature linking changes in FVC to changes in exercise capacity[,]" Dr. Wertheim argues that because the '810 provisional application discloses statistically significant improvement in FVC, then improvement in 6MWD would also be statistically significant and this would in turn cover the full scope of claim 1 of the '327 patent.[208] As explained below, none of the literature cited below supports Dr. Wertheim's proposition that that there is any correlation between FVC and exercise capacity in PH-ILD patients. Further, none of the literature cited by Dr. Wertheim is related to treprostinil. Moreover, the literature is also not based on patients diagnosed with PH-ILD. The papers simply do not support the idea that there is a correlation between FVC and 6MWD in PH-ILD patients treated with inhaled treprostinil. Thus, from a clinical perspective, the publications do not support Dr. Wertheim's opinion that a POSA would understand the treatment methods claimed in the '810 provisional application to cover improvements in exercise.

97. As I have noted in Section III.A-B of my opening report, ILD is a completely different disease from PH-ILD.[209] Damage caused in the lungs by ILD, along with the reduced oxygen availability caused by ILD, can lead to increased pressure in pulmonary circulation, resulting in PH. A POSA would not equate the treatment and study of ILD with that of PH-ILD as a patient suffering from ILD does not necessarily also suffer from PH. Thus, from a clinical perspective, the publications cited by Dr. Wertheim in paragraphs 140-153, 240, and 250 of his report, which pertain to patients with IPL, IPF, and CF, are not relevant to the position that he takes regarding a POSA's understanding of the treatment methods claim in the '810 provisional

[208] Wertheim Rebuttal Report at ¶ 240.
[209] Channick Opening Report at ¶ 19.

application. Dr. Wertheim improperly relies on data pulled from studies conducted in patients in a different disease state than what the '327 patent discloses. I understand that Dr. Ogenstad is addressing the publications cited by Dr. Wertheim from a statistical perspective. I address these articles from a clinical perspective below.

98. I have reviewed Noble 2011, a publication detailing the results of the CAPACITY Trial.[210] The CAPACITY Trial was "designed to confirm the results of a phase 2 study that suggested that pirfenidone, a novel antifibrotic and anti-inflammatory drug, reduces deterioration in lung function in patients with idiopathic pulmonary fibrosis."[211] CAPACITY did not test outcomes in patients administered inhaled treprostinil nor was the aim to test the PH-ILD patient population. The ASCEND Trial, which Dr. Wertheim also cites with respect to his argument that FVC and 6MWD bear a correlation such that the '810 provisional is read to cover the full scope of the '327 patent claim 1, also tested the administration of pirfenidone in the IPF patient population.[212] Thus, for the same reasons that the CAPACITY trial fails to support Dr. Wertheim's arguments, the ASCEND trial similarly fails to provide support. IPF and PH-ILD are not the same disease. Moreover, while the ASCEND trial reported statistically significant results in changes in symptomology for patients receiving pirfenidone versus the placebo, the publication does not address the strength of any purported correlation between 6MWD and FVC.

99. I have reviewed du Bois 2010.[213] The objective of the study detailed in du Bois 2010 was "[t]o assess the reliability, validity, and responsiveness of the 6MWT and estimate the minimal clinically important difference (MCID) in patients with IPF."[214] As noted in the

[210] Noble 2011 (UTC_PH-ILD_220986).
[211] *Id*.
[212] Wertheim Rebuttal Report at ¶ 142.
[213] du Bois 2010 (UTC_PH-ILD_221604).
[214] *Id*. at UTC_PH-ILD_221604.

publication, "Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, interstitial lung disease of unknown etiology."[215] While IPF is a subset of ILD, IPF is not PH-ILD, or a sub-population of PH-ILD. The publication itself differentiates between IPF and PH, noting that "[t]he 6-minute-walk test (6MWT) is a practical and reliable measure of exercise tolerance that is widely used to assess the functional status of patients with a variety of cardiac and pulmonary diseases, including heart failure, ***pulmonary hypertension***, and chronic obstructive pulmonary disease (COPD) . . . [h]owever, studies evaluating the measurement properties of the 6MWT in patients with ***IPF*** have been limited by small sample sizes or narrowly defined patient subsets and, presumably because of these limitations, have generally yielded inconsistent results[.]"[216] Dr. Wertheim's reliance on du Bois 2010 is flawed because the study concerned IPF patients and was completely unrelated to treprostinil administration.

100. The study described in du Bois 2011, titled "Forced Vital Capacity in Patients with Idiopathic Pulmonary Fibrosis[,]" like du Bois 2010, involved neither PH-ILD nor the administration of treprostinil.[217] Thus, for the same reasons that I have listed above that render Dr. Wertheim's analysis based on du Bois 2010, flawed, I also find his analysis based on du Bois 2011 flawed.

101. I have reviewed Swigris 2010, titled "The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference."[218] As with other references Dr. Wertheim cites, Swigris 2010 relates to a study of patients with IPF, not PH-ILD. There is no indication in the study which suggests that the patient population comprised individuals with PH.

[215] *Id*.
[216] *Id*. (emphasis added).
[217] du Bois 2011 (UTC_PH-ILD_221611).
[218] Swigris 2010 (UTC_PH-ILD_221336).

To the contrary, patients were excluded from the study if they had severe pulmonary hypertension.[219] Swigris 2010 is also unrelated to the administration of treprostinil.

102. I have reviewed Nathan 2015, titled "Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis."[220] Nathan 2015 studied patients with IPF, not PH-ILD and like the other references, did not study the administration of treprostinil.

103. I have reviewed Brown 2018, titled "The Value and Application of the 6-Minute-Walk Test in Idiopathic Pulmonary Fibrosis."[221] The Brown 2018 study involved patients with IPF, not PH-ILD and as with the other publications, is not related to the administration of treprostinil. The publication itself notes the prognostic difference between patients with IPF and those with underlying pulmonary hypertension. As noted in the publication, "[a] lower heart rate recovery has been associated with worse outcomes in patients with IPF, with less than or equal to 13 beats at 1 minute being an indicator of underlying pulmonary hypertension and a strong predictor of subsequent mortality[.]"[222] Moreover, Brown 2018 notes that a *post-hoc* analysis of data from the INSPIRE trial showed that "the 6MWT distance and 24-week change in 6MWT distance were closely associated with 1-year mortality, despite ***relatively weak correlations between 6MWT distance and various measures of pulmonary function***[.]"[223] Brown 2018 further concludes that this weak correlation "suggests that the 6MWT may assess a separate, clinically significant domain of the disease process and provide additional information regarding prognosis."[224]

[219] *Id.* at UTC_PH-ILD_221337.
[220] Nathan 2015 (UTC_PH-ILD_220929).
[221] Brown 2018 (UTC_PH-ILD_220101).
[222] *Id*. at UTC_PH-ILD_220104.
[223] *Id.* at UTC_PH-ILD_220102 (emphasis added).
[224] *Id*.

104. I have reviewed Nishiyama 2016, titled "Pulmonary Hemodynamics and Six-Minute Walk Test Outcomes in Patients with Interstitial Lung Disease."[225] Of the 46 patients with ILD included in the Nishiyama 2016 study, none of who were treated with treprostinil, there were only 2 patients "whose mean PAP was ≧25 mmHg, high enough to be diagnosed with pulmonary hypertension[.]"[226] Nishiyama 2016 further explains that "some patients with pulmonary hypertension could have been be excluded from [the] study, because patients with long-term oxygen therapy who could not discontinue[] their oxygen apparatus at the time of 6MWT and RHC examinations both were excluded from the study[,]" and that "[i]t can be assumed in clinical practice that the presence of pulmonary hypertension should be investigated separately from evaluations for pulmonary function and exercise capacity in ILD patients."[227] Nishiyama 2016 was therefore not directed to treprostinil therapies in the PH-ILD patient population.

105. I have reviewed Oldham 2018, titled "Network Analysis to Risk Stratify Patients With Exercise Intolerance."[228] The objective of Oldham 2018 was to "[u]se unbiased analyses to identify variables that correspond to clinical risk in patients with exercise intolerance."[229] As such, the patient population included a wide range of patients in various non-disease or disease states. The primary clinical indication for the studies identified "was unexplained exertional intolerance, which encompasses dyspnea on exertion, fatigue, or lightheadedness."[230] As with the aforementioned publications, the purpose of Oldham 2018 was not to study PH-ILD nor did the analysis have anything to do with inhaled treprostinil.

[225] Nishiyama 2016 (UTC_PH-ILD_220979).
[226] *Id*. at UTC_PH-ILD_220981.
[227] *Id*. at UTC_PH-ILD_220982.
[228] Oldham 2018 (UTC_PH-ILD_220996).
[229] *Id*.
[230] *Id*. at UTC_PH-ILD_220999.

106. I have reviewed Fell 2009, titled "The Prognostic Value of Cardiopulmonary Exercise Testing in Idiopathic Pulmonary Fibrosis."[231] As noted in the publication, there were "several limitations to this study[,]" including the fact that "[p]atients in this study were not evaluated for the presence of pulmonary hypertension."[232] Here, again, Dr. Wertheim fails to sufficiently explain how a publication which admittedly lacks analysis related to pulmonary hypertension, would be understood by a POSA to relate to PH-ILD such that a conclusion can be drawn regarding the correlation between measurements of FVC and exercise capacity in patients with PH-ILD.

107. Dr. Nathan argues that Faria-Urbina 2018 fails to disclose the asserted claims because "it mixes PH-ILD patients with a broader patient pool[.]"[233] Dr. Nathan's argument that Agarwal 2015 "does not necessarily and inevitably" practice the claims because it "does not describe any particular patient as having PH-ILD[,]" is made in the same vein.[234] Whereas Faria-Urbina 2018 and Agarwal 2015 do study the impact of administering inhaled treprostinil to PH-ILD patients on their exercise capacity, Dr. Wertheim's publications are not directed at the PH-ILD population.

108. Dr. Wertheim has provided no evidence that there is any correlation between FVC and exercise capacity in PH-ILD patients. Accordingly, and contrary to Dr. Wertheim's opinion, a POSA reviewing the FVC data in the '810 application would not conclude that the inventors were in possession of a method of improving the exercise capacity of a PH-ILD patient through the administration of inhaled treprostinil.

[231] Fell 2009 (UTC_PH-ILD_220279).
[232] *Id*. at UTC_PH-ILD_220282.
[233] Nathan Rebuttal Report at ¶ 372.
[234] *Id*. at ¶ 497.

F. FVC and The Pathophysiology of PH-ILD

109. Dr. Wertheim supports his argument that a POSA "would know that FVC is a well established means of monitoring . . . destruction of lung function and would further appreciate exacerbations' role in accelerating this lung function" by noting that "FVC is used to diagnose PH-ILD and well-established criterion for inclusion and exclusion in clinical trials."[235]

110. FVC is not used to diagnose PH-ILD. In my research and clinical practice, the diagnosis of PH-ILD involves the diagnosis of the PH component and the diagnosis of the ILD component. As I noted in my Opening Expert Report, PH is diagnosed by measuring mean pulmonary arterial pressure ("mPAP").[236] As I further noted, mean arterial pressure is measured using a technique called right heart catheterization.[237] The diagnosis of ILD requires the detection of changes in the lung's structure, which can be discovered using x-rays, CT scans, and, in some cases, bronchoscopies and lung biopsies. I am not aware, and Dr. Wertheim has provided no support for his contention that FVC is used to diagnose PH-ILD, or PH.

G. FVC as a Safety Endpoint

111. Dr. Wertheim argues that the fact that FVC is commonly used as a safety endpoint "does not mean that it has no relevance to efficacy or exercise capacity in the context of Example 1."[238] Dr. Wertheim supports his argument by noting that the inventors "did not testify that there were 'no data showing improvements in exercise capacity[.]'"[239] But this is the wrong inquiry. First, Dr. Wertheim points to no inventor testimony where they do say the '810 application discloses data associated with exercise capacity. Second, Dr. Wertheim has failed to show that

[235] Wertheim Rebuttal Report at ¶ 252.
[236] Channick Opening Report at ¶ 13.
[237] *Id*. I also note that if a POSA were to review the INCREASE study, FVC was not used to diagnose PH or PH-ILD. *See* 2017 INCREASE Protocol (UTC_PH-ILD_105083) at UTC_PH-ILD_10508-89.
[238] Wertheim Rebuttal Report at ¶¶ 250-251.
[239] *Id*. at ¶ 251.

FVC bears a correlation to exercise capacity in PH-ILD patients such that a POSA would understand the '810 provisional to disclose the inventors were in possession of the invention in claim 1 of the '327 patent. Dr. Wertheim himself notes that Dr. Peterson indicated that FVC may have "an ***indirect relationship*** to exercise capacity."[240] An "indirect relationship" is not a correlation as Dr. Wertheim attempts to make it be. Dr. Wertheim further notes that Dr. Smith described FVC as a "surrogate" to the "clinical condition of a patient."[241] However, Dr. Smith, along with the other inventors, also clearly distinguished the use of FVC as a safety endpoint.[242] FVC and exercise capacity are not synonymous with one another and are two distinct measurements, a point supported by the fact that they played different roles in the INCREASE trial. In fact, even in the INCREASE trial, Dr. Nathan described the results related to pulmonary function, including FVC as merely hypothesis generating, further supporting the lack of any correlation between the two.[243]

112. Dr. Wertheim argues that "[w]hile Dr. Waxman and the inventors acknowledged that FVC was employed as a safety endpoint in INCREASE, they did not testify that FVC could not be used to assess exercise capacity[.]"[244] But they also did not testify they could be. And importantly, all the inventors testified that they had not made the invention of the '327 patent until the INCREASE study data was released—data that directly measured 6MWD and thus exercise capacity. Moreover, Dr. Waxman testified, which Dr. Wertheim ignores, that FVC is not used as an efficacy endpoint in the INCREASE study:

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[240] *Id*. at ¶ 251 n.448 (emphasis added).
[241] *Id*.
[242] Smith Depo. Tr. at 55:23-57:1; Waxman Depo. Tr. at 154:18-155:3 ("Q: Why is FVC a safety endpoint? A: FVC is used in interstitial lung disease studies, and if we saw a decline in FVC, it would raise concerns from a safety standpoint. Q: Is FVC used as efficacy endpoints in this INCREASE study? A: No."); *id.* at 155:7-14; (Q: Is FVC a measure of exercise capacity or tolerance? [objection omitted] A: We talked about FVC much earlier in this deposition and we defined it as a lung volume measurement."); *see also* Waxman Depo. Tr. at 106:8-19.
[243] Nathan 2021 (LIQ_PH-ILD_00000216).
[244] Wertheim Rebuttal Report at ¶ 251.

Q. Is FVC used as an efficacy endpoint in this INCREASE study?
A. No.[245]

H. Priority for the Dependent Claims

113. Claims 2, 6-11, and 14-16 all depend from claim 1.[246] Because the '327 patent inventors were not in possession of the invention claimed in claim 1 as of the April 2020, they also cannot be in possession of the invention claimed in dependent claims 2, 6-11, and 14-16. As with claim 1, Dr. Wertheim improperly attempts to read INCREASE into the '810 provisional such that the claims 2, 6-11, and 14-16 of the '327 patent would have also been disclosed. For the same reasons as I have noted in Section V.C above, a POSA reading the '810 provisional would not understand the provisional application to disclose INCREASE and moreover, counsel has informed me that turning to information outside the specification of the '810 provisional application is not permitted when determining whether written description is demonstrated for the purpose of priority.

114. Claim 2 requires a "statistically significant" change in 6MWD while claims 6-11 and 14-16 require varying degrees of demonstrated improvements in 6MWD such as an increase of "10 m after 8 weeks, 12 weeks, or 16 weeks."[247] Claims 6-8 also require "statistically significant" reductions in exacerbations of interstitial lung disease and clinical worsening events."[248]

115. With respect to claim 2, Dr. Wertheim argues statistically significant improvements in percent predicted FVC and a statistically significant reductions in acute exacerbations would lead a POSA to conclude that there would have been a statistically significant improvement in

[245] Waxman Depo. Tr. at 155:1-3.
[246] '327 patent at cls. 1, 2, 6-11, 14-16.
[247] *Id*. at cls. 2, 6-11, and 14-16.
[248] *Id*. at cls. 6-8.

included hospitalization for cardiopulmonary indication or decrease in 6MWD by more than 10% compared to baseline."[264] However, claim 8 requires a decrease in 6MWD "by more than 15% compared [to] baseline[.]"[265] Dr. Wertheim goes on to address enablement in this paragraph, which I understand is a completely different legal issue.

122. Moreover, Dr. Wertheim provides no support for his assertion that there is a "causal relationship . . . between the FVC and exacerbation data reported in Example 1 and the particular clinical worsening events described in claim 8 of the '327 patent[,]" that would lead a POSA to conclude that the inventors were in possession of the method described in claim 8 of the '327 patent.[266] Dr. Wertheim cites three publications to support his proposition that "a POSA would understand that acute exacerbations of underlying lung disease typically result in hospitalizations for PH-ILD patients[,]" yet none of these publications report results in the PH-ILD patient population, let alone discuss any purported "causal relationship" between FVC and "hospitalization for cardiopulmonary indication" or decrease in 6MWD "by more than 15% compared a baseline."[267]

123. Claim 9 of the '327 patent depends from claim 1 and, as such, a POSA would not conclude the inventors were in possession of the invention of dependent claim 9. Claim 9 further requires that administration of treprostinil result in "statistically significant improve[ment] of forced vital capacity (FVC) in the patient after 8 weeks, 12[] weeks, or 16 weeks[.]"[268] As discussed in my Opening Report, claim 9 is directed to both absolute and percent predicted FVC.[269] The results described in the '810 provisional reference percent predicted FVC which is not the

[264] *Id*. at ¶ 304.
[265] '327 patent at cl. 8.
[266] Wertheim Rebuttal Report at ¶ 305.
[267] *Id*. at ¶ 302 & n.526 (citing Kolb 2018a; Collard 2016; Moua 2016).
[268] '327 patent at cl. 9.
[269] Channick Opening Report at ¶¶ 427-428.

same as absolute FVC, and thus a POSA would not conclude that the inventors were in possession of the full scope of the invention claimed in claim 9. Further, the statistically significant result in FVC is required for the claimed "PH-ILD" patient population, but again, as discussed in my Opening Report, statistically significant results were not obtained for the PH-ILD ITT population, but only sub-populations. Thus, the data in Example 1 would not convey to a POSA that the inventors were in possession of the invention of the full scope of claim 9. Dr. Wertheim tries to address this by aggregating data from Tables 1-3 and concluding that "[b]ased on the data reported in Example 1 of the '810 Provisional Application, discussed above, a POSA would understand that, on average, ***all patients*** showed a statistically significant improvement in % predicted FVC as compared to placebo at both the 8 week and 16 week time points[.]"[270] This is not what Example 1 shows as it is clear that the ITT population, which is all of the patients, did not achieve a statistically significant result. In fact, it is clear from the data in the Lancet publication supplement that 46% of patients in the ITT group actually had worse FVC at week 16 as compared to baseline.[271]

124. Claim 10 of the '327 patent depends from claim 9 and additionally requires that the administration of treprostinil to the PH-ILD patient improve the patient's FVC "by at least 20 mL after 8 weeks, 12 weeks, or 16 weeks of the administering."[272] Dr. Wertheim argues that a POSA would not understand this claim to require that the improvement in FVC be statistically significant.[273] But claim 10 ***depends*** from claim 9, indicating that the improvement in FVC disclosed in claim 10 must be both statistically significant ***and*** "at least 20 mL after 8 weeks, 12

[270] Wertheim Rebuttal Report at ¶ 315.
[271] Nathan 2021 (LIQ_PH-ILD_00000216).
[272] '327 patent at cl. 10.
[273] Wertheim Rebuttal Report at ¶ 330.

weeks, or 16 weeks of the administering."[274] Dr. Wertheim states that "a POSA would understand that claim 10 of the '327 patent could be satisfied if the improvement in [the] percent predicted FVC was statistically significant but the improvement in absolute FVC was not."[275] This is at odds with claim 10, which recites "at least 20 mL." This is an absolute FVC measurement, not a percent predicted measurement, and it is unclear from Dr. Wertheim's report how a statistically significant change in percent predicted FVC demonstrates the same result for absolute FVC when the data in Example 1 proves otherwise.

125. Claim 11 depends from claim 1 and additionally requires that the administration of inhaled treprostinil to the PH-ILD patient be "performed by a pulsed inhalation device."[276] With respect to claim 11, Dr. Wertheim opines that "the disclosures of the '810 Provisional Application provide sufficient written description and enablement to support every limitation of claim 1 of the '327 patent."[277] For the same reasons I discuss in my Opening Report and in this report in ¶¶ 88-112, a POSA would not conclude the inventors were in possession of the invention of claim 1 based on the disclosures of the '810 provisional application. Dr. Wertheim's opinions as to claim 11 do not provide any additional support to demonstrate that a POSA would understand the inventors to have been in possession of claim 1. As claim 11 depends from claim 1, a POSA would not conclude that the inventors were in possession of the invention of claim 11 at the time the '810 provisional was filed.

126. Claim 14 depends from claim 11 and additionally requires that the "pulsed inhalation device" used to administer the inhaled treprostinil be "a dry powder inhaler comprising

[274] '327 patent at cl. 10.
[275] Wertheim Rebuttal Report at ¶ 330 n.569.
[276] '327 patent at cl. 11.
[277] Wertheim Rebuttal Report at ¶ 341.

invention of claim 1. As claim 16 depends from claim 15, a POSA would not conclude that the inventors were in possession of the invention of claim 16.

I. Dr. Wertheim's Conclusion Regarding Correlations Between 6MWD and FVC Further Supports that the Prior Art Discloses the Invention

134. 6MWD, which is the distance that a patient can walk in six minutes, is a standard measure of exercise capacity in PH patients. FVC measures the amount of air that an individual is able to forcibly exhale from their lungs. FVC is not a measure of exercise capacity. Claim 1 of the '327 patent requires an improvement in exercise capacity, which is not demonstrated by FVC. However, if I assume Dr. Wertheim's position that FVC and 6MWD data are correlated such that the '810 provisional application would convey to a POSA that the inventors were in possession of improving the exercises capacity of a PH-ILD patient by administering inhaled treprostinil, then the prior art's disclosure of statistically significant improvements in 6MWD would render claims 9 and 10 of the '327 patent, which are directed to FVC, invalid.

135. Dr. Wertheim argues that the "correlation between exercise capacity and FVC would make . . . sense to the POSA, particularly in the context of PH-ILD" because "[p]atients diagnosed with PH-ILD typically have significantly impaired lung function, characterized by percent predicted FVC values of 70% or less[.]"[288] Dr. Wertheim supports this argument by citing Faria-Urbina 2018.[289]

136. The authors of Faria-Urbina 2018 reported that the patients experienced a "significant improvement in . . . 6-min walk distance (n=11, 243±106 vs. 308±109; p=0.022),"[290] which led the authors to conclude that, for "patients with Group 3 PH treated with [inhaled treprostinil,] . . . therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT

[288] Wertheim Rebuttal Report at ¶ 241.
[289] *Id*.
[290] Faria-Urbina 2018 (UTC_PH-ILD_009936) at UTC_PH-ILD_009936.

distance[.]"[291] According to Dr. Nathan, Faria-Urbina 2018 reported that "there was no significant change in FVC based on treprostinil administration," despite the aforementioned significant improvement in 6MWT distance.[292]

137. Thus, Dr. Wertheim's argument that Faria-Urbina 2018 supports the notion that "the data in the literature would tell the POSA that if an improvement in FVC was observed, the POSA could also expect an improvement in exercise capacity[,]"[293] runs contrary to Dr. Nathan's assertion that Faria-Urbina 2018 fails to anticipate the '327 patent based on the fact that the results in Faria-Urbina 2018 demonstrate no significant change in FVC.[294] A POSA cannot both interpret Example 1 of the '810 provisional application as disclosing an improvement in exercise capacity based on an improvement in FVC and simultaneously believe, in light of the improved 6MWD demonstrated in Faria-Urbina 2018, that Faria-Urbina 2018 fails to anticipate and render obvious the asserted claims of the '327 patent directed to FVC.

J. Dr. Wertheim does not address priority date with respect to claims 3-5 and 17-19

138. In my Opening Report, I address the priority date with respect to claims 1-11 and 14-19 of the '327 patent.[295] Dr. Wertheim does not offer any opinion in his Rebuttal Report as to the priority date of claims 3-5 and 17-19 of the '327 patent.[296]

[291] Faria-Urbina 2018 (UTC_PH-ILD_009936) at UTC_PH-ILD_009939; *see also* Waxman Depo. Tr. at 102:17-23.
[292] Nathan Rebuttal Report at ¶ 183.
[293] Wertheim Rebuttal Report at ¶ 241.
[294] Nathan Rebuttal Report at ¶ 415.
[295] Channick Opening Report at ¶¶ 74-93.
[296] *See* Wertheim Rebuttal Report at ¶ 1, footnote 1 ("UTC has not asked me to assess the priority date of claims 3-5, 12, 13, and 17-19 of the '327 patent, and I offer no opinions in this regard below.").